



40.00-101-A
817548

N/40174

SPECIFICATION

FOR

PATENT APPLICATION

IN

UNITED STATES OF AMERICA

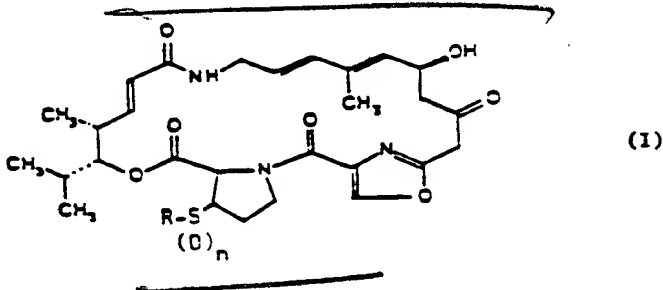
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assignors to Rhone-Poulenc Sante

"PRISTINAMYCIN II_B DERIVATIVES, THEIR PREPARATION, AND
COMPOSITIONS CONTAINING THEM"

Sup This invention relates to pristinamycin II_B derivatives
their preparation, and compositions containing them.

The present invention provides new pristinamycin
II_B derivatives, of the formula:



B and their acid addition salts, in which R denotes: either
a nitrogen-containing 4 to 7-membered heterocyclic ring
radical, which may contain 1 or more other hetero atoms
chosen from nitrogen, oxygen and sulphur in the form of
sulphoxide or sulphone, and unsubstituted or substituted
10 by alkyl; or alkyl of 2 to 4 carbon atoms substituted by
1 or 2 radicals chosen from phenyl, cycloalkylamino of
3 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6
ring atoms, alkylamino, dialkylamino and dialkylcarbamoyloxy,
the alkyl parts of these 2 latter radicals being unjoined
15 or joined to form, with the nitrogen atom to which they
are attached, a saturated or unsaturated 4 to 7-membered
heterocyclic ring which may contain another hetero atom
chosen from nitrogen, oxygen and sulphur in the form of
sulphoxide or sulphone, and unsubstituted or substituted by
20 alkyl, or alkyl of 2 to 4 carbon atoms substituted by one
or more nitrogen-containing, 4 to 7-membered heterocyclic
25 rings which may contain 1 or 2 other hetero atoms chosen

from nitrogen, oxygen and sulphur in the form of sulfoxide or sulphone, and unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl by a carbon atom of the ring, at least one of the substituents carried by the said alkyl chain being a nitrogen-containing
5 substituent capable of forming salts, and n is 1 or 2. The alkyl radicals and moieties referred to above are linear or branched and, unless mentioned otherwise, contain 1 to 10 carbon atoms.

P The products of formula (I) have isomeric forms and their isomers and their mixtures are included within the
10 scope of the present invention.

When R denotes a heterocyclic radical, this radical can be, for example: 3-azetidiny1, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl.

When R denotes an alkyl radical substituted by a
15 heterocyclic ring radical, the heterocyclic ring radical can be chosen, for example, from the radicals listed above or the 2-azetidiny1, 2-pyrrolidinyl, 2-piperidyl, 2-azepinyl, piperazinyl, 4-alkylpiperazinyl, quinolyl, isoquinolyl or imidazolyl radicals.

20 When R contains a dialkylamino or dialkylcarbamoyloxy radical in which the alkyl moieties form a heterocyclic ring with the nitrogen atom to which they are

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attached, this ring can be chosen, for example, from:

1-azetidiny, 1-pyrrolidinyl, piperidino, 1-azepinyl,
morpholino, thiomorpholino in the form of sulfoxide or
sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-
5 1-homopiperazinyl, or 1-imidazolyl.

The following compounds of general formula (I) can be
mentioned, in particular, by way of example:

- 26-(3-azetidiny)sulphinylpristinamycin II_B
- 26-(1-methyl-3-azetidiny)sulphinylpristinamycin II_B
- 10 26-(1-ethyl-3-azetidiny)sulphinylpristinamycin II_B
- 26-(1-isopropyl-3-azetidiny)sulphinylpristinamycin II_B
- 26-(3-pyrrolidinyl)sulphinylpristinamycin II_B
- 26-(1-methyl-3-pyrrolidinyl)sulphinylpristinamycin II_B
- 26-(1-ethyl-3-pyrrolidinyl)sulphinylpristinamycin II_B
- 15 26-(1-isopropyl-3-pyrrolidinyl)sulphinylpristinamycin II
- 26-(3-piperidyl)sulphinylpristinamycin II_B
- 26-(1-methyl-3-piperidyl)sulphinylpristinamycin II_B
- 26-(1-ethyl-3-piperidyl)sulphinylpristinamycin II_B
- 26-(4-piperidyl)sulphinylpristinamycin II_B
- 20 26-(1-methyl-4-piperidyl)sulphinylpristinamycin II_B
- 26-(1-ethyl-4-piperidyl)sulphinylpristinamycin II_B
- 26-(3-azepinyl)sulphinylpristinamycin II_B
- 26-(4-azepinyl)sulphinylpristinamycin II_B
- 26-(2-cyclopropylaminoethyl)sulphinylpristinamycin II_B
- 25 26-(2-cyclobutylaminoethyl)sulphinylpristinamycin II_B
- 26-(2-cyclopentylaminoethyl)sulphinylpristinamycin II_B
- 26-(2-cyclohexylaminoethyl)sulphinylpristinamycin II_B

- 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-(2-methylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-ethylaminoethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-propylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-butylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 10 - 26-(dimethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylaminoethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-diisobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 20 - 26-(2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-morpholinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 25 - 26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphonylpristinamycin IIg

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P) 26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin II_B
P) 26-(2-dimethylaminocarbamoyloxyethyl)sulphonylpristinamycin II_B
- 26-(2-diethylaminocarbamoyloxyethyl)sulphonylpristinamycin II_B
5
P) 26-(2-diisopropylaminocarbamoyloxyethyl)sulphonylpristinamycin II_B
P) 26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphonylpristinamycin II_B
P) 10 26-[2-(2-azetidiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(3-azetidiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(2-pyrrolidiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(3-pyrrolidiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(2-piperidyl)ethyl]sulphonylpristinamycin II_B
15 26-[2-(3-piperidyl)ethyl]sulphonylpristinamycin II_B
- 26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin II_B
- 26-[2-(2-azepiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(3-azepiny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(4-azepiny)ethyl]sulphonylpristinamycin II_B
20 26-[2-(3-quinoly)ethyl]sulphonylpristinamycin II_B
- 26-[2-(4-quinoly)ethyl]sulphonylpristinamycin II_B
- 26-[2-(1,2,3,4-tetrahydro-2-isoquinoly)ethyl]-sulphonylpristinamycin II_B
- 26-[2-(1-isoquinoly)ethyl]sulphonylpristinamycin II_B
25 26-(2-imidazolylethyl)sulphonylpristinamycin II_B
26-(2-cyclopropylamino-1-methylethyl)sulphonylpristinamycin II_B

- 26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopentylamino-1-methylethyl)sulphonylpristinamycin IIg
- 5 - 26-(cyclohexylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-cyclohexyl-N-methyl-amino)-1-methylethyl]-sulphonylpristinamycin IIg
- 26-(2-methylamino-1-methylethyl)sulphonylpristinamycin
- 10 IIg
- 26-(2-ethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(1-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-isopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-butylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 20 - 26-(1-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-diisopropylamino-1-methylethyl)sulphinylpristinamycin IIg
- 26-(2-dibutylamino-1-methylethyl)sulphinylpristinamycin IIg
- 5 - 26-(2-diisobutylamino-1-methylethyl)sulphinylpristinamycin IIg
- 26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl]sulphinylpristinamycin IIg
- 26-[2-(1-azetidiny1)-1-methylethyl]sulphinylpristinamycin IIg
- 10 - 26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin IIg
- 26-(1-methyl-2-piperidinoethyl)sulphinylpristinamycin IIg
- 15 - 26-[2-(1-azepinyl)-1-methylethyl]sulphinylpristinamycin IIg
- 26-(1-methyl-2-morpholinoethyl)sulphinylpristinamycin IIg
- 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphinylpristinamycin IIg
- 20 - 26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphinylpristinamycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphinylpristinamycin IIg
- 25 - 26-[2-(1-imidazolyl)-1-methylethyl]sulphinylpristinamycin IIg

- 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin II_B
- 26-(2-diethylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin II_B
- 5 - 26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin II_B
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphinylpristinamycin II_B
- 26-[2-(2-azetidiny)l-1-methylethyl]sulphinylpristinamycin II_B
- 10 - 26-[2-(3-azetidiny)l-1-methylethyl]sulphinylpristinamycin II_B
- 26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristinamycin II_B
- 15 - 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin II_B
- 26-[1-methyl-2-(2-piperidyl)ethyl]sulphinylpristinamycin II_B
- 26-[1-methyl-2-(3-piperidyl)ethyl]sulphinylpristinamycin II_B
- 20 - 26-[1-methyl-2-(4-piperidyl)ethyl]sulphinylpristinamycin II_B
- 26-[2-(2-azepiny)l-1-methylethyl]sulphinylpristinamycin II_B
- 25 - 26-[2-(3-azepiny)l-1-methylethyl]sulphinylpristinamycin II_B

26-[2-(4-azepinyl)-1-methylethyl]sulphinylpristinamycin
II_B

26-[1-methyl-2-(3-quinolyl)ethyl]sulphinylpristinamycin II_B

5 26-[1-methyl-2-(4-quinolyl)ethyl]sulphinylpristinamycin II_B

26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphinylpristinamycin II_B

10 26-[2-(1-isoquinolyl)-1-methylethyl]sulphinylpristinamycin II_B

26-(2-imidazolyl-1-methylethyl)sulphinylpristinamycin II_B

26-(2-cyclopropylamino-2-methylethyl)sulphinylpristinamycin II_B

15 26-(2-cyclobutylamino-2-methylethyl)sulphinylpristinamycin II_B

26-(2-cyclopentylamino-2-methylethyl)sulphinylpristinamycin II_B

26-(2-cyclohexylamino-2-methylethyl)sulphinylpristinamycin II_B

20 26-[2-(N-cyclohexyl-N-methylamino)-2-methylethyl]-sulphinylpristinamycin II_B

26-(2-methylamino-2-methylethyl)sulphinylpristinamycin II_B

25 26-(2-ethylamino-2-methylethyl)sulphinylpristinamycin II_B

26-(2-methyl-2-propylaminoethyl)sulphinylpristinamycin II_B

- 26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-butylamino-2-methylethyl)sulphonylpristinamycin II_B
- 5 26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin II_B
- 10 26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin II_B
- 15 26-(2-diisopropylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin II_B
- 26-(2-diisobutylamino-2-methylethyl)sulphonylpristinamycin II_B
- 20 26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]sulfinylpristinamycin II_B
- 26-[2-(1-azetidinyI)-2-methylethyl]sulphonylpristinamycin II_B
- 25 26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B
- 26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin II_B

- 1) 3 26-[2-(1-azepinyl)-2-methylethyl]sulphinylpristinamycin
IIg 7
- 1) 3 26-(2-methyl-2-morpholinoethyl)sulphinylpristinamycin
IIg
- 5 5 26-[2-methyl-2-(1-piperazinyl)ethyl]sulphinylpristina-
mycin IIg
- 1) 3 26-[2-(4-methyl)-1-piperazinyl]-2-methylethyl]sulphinyl-
pristinamycin IIg 9
- 1) 3 26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]sulphinyl-
10 pristinamycin IIg 1
- 1) 3 26-[2-(1-imidazolyl)-2-methylethyl]sulphinylpristina-
mycin IIg 9
- 1) 3 26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphinyl-
pristinamycin IIg
- 15 3 26-(2-diethylaminocarbamoyloxy-2-methylethyl)sulphinyl-
pristinamycin IIg
- 10 3 26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)sulphinyl-
pristinamycin IIg
- 1) 3 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methyl-
20 ethyl]sulphinylpristinamycin IIg
- 1) 3 26-[2-(2-azetidiny)-2-methylethyl]sulphinylpristina-
mycin IIg
- 1) 3 26-[2-(3-azetidiny)-2-methylethyl]sulphinylpristina-
mycin IIg
- 25 3 26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristina-
mycin IIg

- 26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B 9
 - 26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin II_B 1
 - 5) - 26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin II_B 1
 - 26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin II_B 1
 - 26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B 1
 - 10 - 26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B 1
 - 26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B 1
 - 15 - 26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin II_B 1
 - 26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin II_B 1
 - 26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin II_B 1
 - 20 - 26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin II_B 9
 - 26-(imidazolyl-2-methylethyl)sulphonylpristinamycin II_B
 - 25 - 26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin II_B
 - 26-(2-dimethylaminobutyl)sulphonylpristinamycin II_B
- M

- 10
- 26-(3-azetidinyI)sulphonylpristinamycin II_B
 - 26-(1-methyl-3-azetidinyI)sulphonylpristinamycin II_B
 - 26-(1-ethyl-3-azetidinyI)sulphonylpristinamycin II_B
 - 26-(1-isopropyl-3-azetidinyI)sulphonylpristinamycin II_B
 - 5
 - 26-(3-pyrrolidinyl)sulphonylpristinamycin II_B
 - 26-(1-methyl-3-pyrrolidinyl)sulphonylpristinamycin II_B
 - 26-(1-ethyl-3-pyrrolidinyl)sulphonylpristinamycin II_B
 - 26-(1-isopropyl-3-pyrrolidinyl)sulphonylpristinamycin

II_B

- 10
- 26-(3-piperidyl)sulphonylpristinamycin II_B
 - 26-(1-methyl-3-piperidyl)sulphonylpristinamycin II_B
 - 26-(1-ethyl-3-piperidyl)sulphonylpristinamycin II_B
 - 26-(4-piperidyl)sulphonylpristinamycin II_B
 - 26-(1-methyl-4-piperidyl)sulphonylpristinamycin II_B
 - 15
 - 26-(1-ethyl-4-piperidyl)sulphonylpristinamycin II_B
 - 26-(3-azepinyl)sulphonylpristinamycin II_B
 - 26-(4-azepinyl)sulphonylpristinamycin II_B
 - 26-(2-cyclopropylaminoethyl)sulphonylpristinamycin II_B
 - 26-(2-cyclobutylaminoethyl)sulphonylpristinamycin II_B
 - 20
 - 26-(2-cyclopentylaminoethyl)sulphonylpristinamycin II_B
 - 26-(2-cyclohexylaminoethyl)sulphonylpristinamycin II_B
 - 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphonylpris-

tinamycin II_B

- 10
- 26-(2-methylaminoethyl)sulphonylpristinamycin II_B
 - 25
 - 26-(2-ethylaminoethyl)sulphonylpristinamycin II_B
 - 26-(2-propylaminoethyl)sulphonylpristinamycin II_B
 - 26-(2-isopropylaminoethyl)sulphonylpristinamycin II_B

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- 1) 26-(2-butylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylaminoethyl)sulphonylpristinamycin IIg
- 5 26-(2-diethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisobutylaminoethyl)sulphonylpristinamycin IIg
- 10 26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-pyrrolidiny)ethyl]sulphonylpristinamycin IIg
- 15 26-(2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepiny)ethyl]sulphonylpristinamycin IIg
- 26-(2-morpholinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-piperaziny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperaziny)ethyl]sulphonylpristinamycin IIg
- 20 26-[2-(4-methyl-1-homopiperaziny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-dimethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 25 26-(2-diethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg

- 26-(2-diisopropylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphonylpristinamycin IIg
- 5 26-[2-(2-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-pyrrolidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-pyrrolidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg]
- 10 - 26-[2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azepiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-azepiny)ethyl]sulphonylpristinamycin IIg
- 15 - 26-[2-(3-quinoly)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-quinoly)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1,2,3,4-tetrahydro-2-isoquinoly)ethyl]sulphonylpristinamycin IIg
- 8.9 26-[2-(1-isoquinoly)ethyl]sulphonylpristinamycin IIg
- 20 26-(2-imidazolylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 20 26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 25 26-(2-cyclopentylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-cyclohexylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-[2-(N-cyclohexyl-N-methylamino)-1-methylethyl]-sulphonylpristinamycin IIg

✓ 26-(2-methylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-ethylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(1-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg

✓ 26-(2-isopropylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-butylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-isobutylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(1-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg

✓ 26-(2-dimethylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-diisopropylamino-1-methylethyl)sulphonylpristinamycin IIg

✓ 26-(2-dibutylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-diisobutylamino-1-methylethyl)sulphonylpristinamycin II_B
- 26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl]sulphonylpristinamycin II_B
- 5 - 26-[2-(1-(azetidiny)-1-methylethyl]sulphonylpristinamycin II_B
- 26-[1-methyl-2-(1-pyrrolidiny)ethyl]sulphonylpristinamycin II_B
- 26-(1-methyl-2-piperidinoethyl)sulphonylpristinamycin II_B
- 10 - 26-[2-(1-azepiny)-1-methylethyl]sulphonylpristinamycin II_B
- 26-(1-methyl-2-morpholinoethyl)sulphonylpristinamycin II_B
- 15 - 26-[1-methyl-2-(1-piperaziny)ethyl]sulphonylpristinamycin II_B
- 26-[2-(4-methyl-1-piperaziny)-1-methylethyl]sulphonylpristinamycin II_B
- 26-[2-(4-methyl-1-homopiperaziny)-1-methylethyl]-sulphonylpristinamycin II_B
- 20 - 26-[2-(1-imidazolyl)-1-methylethyl]sulphonylpristinamycin II_B
- 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphonylpristinamycin II_B
- 25 - 26-(2-diethylaminocarbamoyloxy)-1-methylethyl-sulphonylpristinamycin II_B

- 26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)-sulphonylpristinamycin IIg
 - 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphonylpristinamycin IIg
 - 105 6 26-[2-(2-azetidiny)-1-methylethyl]sulphonylpristinamycin IIg
 - 10 26-[2-(3-azetidiny)-1-methylethyl]sulphonylpristinamycin IIg
 - 10 26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
 - 10 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
 - 10 26-[1-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
 - 105 26-[1-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
 - 10 26-[1-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
 - 10 26-[2-(2-azepiny)-1-methylethyl]sulphonylpristinamycin IIg
 - 20 26-[2-(3-azepiny)-1-methylethyl]sulphonylpristinamycin IIg
 - 10 26-[2-(4-azepiny)-1-methylethyl]sulphonylpristinamycin IIg
 - 105 26-[1-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg
- 70

- 26-[1-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin IIg
- 5 26-[2-(1-isoquinolyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-(2-imidazolyl-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 10 26-(2-cyclobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopentylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclohexylamino-2-methylethyl)sulphonylpristinamycin IIg
- 15 26-[2-(N-cyclohexyl-N-methyl-amino)-2-methylethyl]-sulphonylpristinamycin IIg
- 26-(2-methylamino-2-methylethyl)sulphonylpristinamycin IIg
- 20 26-(2-ethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 25 26-(2-butylamino-2-methylethyl)sulphonylpristinamycin IIg

- 26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 10 - 26-(2-diisopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-diisobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(1-azetidinyI)-2-methylethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg

- 26-(2-methyl-2-morpholinoethyl)sulphonylpristinamycin
IIg

- 26-[2-methyl-2-(1-piperazinyl)ethyl]sulphonylpristina-
mycin IIg

5 - 26-[2-(4-methyl-1-piperazinyl)-2-methylethyl]sulphonyl-
pristinamycin IIg

- 26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]-
sulphonylpristinamycin IIg

10 - 26-[2-(1-imidazolyl)-2-methylethyl]sulphonylpristina-
mycin IIg

- 26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphonyl-
pristinamycin IIg

- 26-(2-diethylaminocarbamoyloxy-2-methylethyl)sulphonyl-
pristinamycin IIg

15 - 26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)-
sulphonylpristinamycin IIg

- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methyl-
ethyl]sulphonylpristinamycin IIg

20 - 26-[2-(2-azetidiny)l)-2-methylethyl]sulphonylpristina-
mycin IIg

- 26-[2-(3-azetidiny)l)-2-methylethyl]sulphonylpristina-
mycin IIg

- 26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristina-
mycin IIg

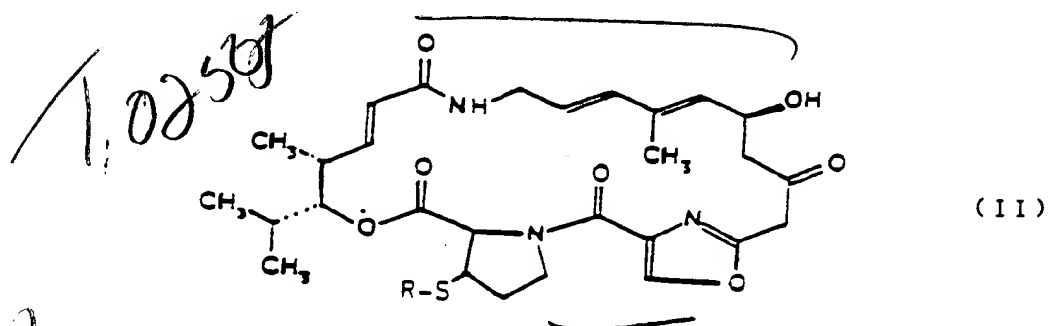
25 - 26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristina-
mycin IIg

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- 1) - 26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
- 1) - 26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 5) - 26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 1) - 26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 1) - 26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 10) - 26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 1) - 26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg
- 15) - 26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 1) - 26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin IIg
- 1) - 26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin IIg
- 20) - 26-(2-imidazolyl-2-methylethyl)sulphonylpristinamycin IIg
- 1) - 26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin IIg
- 25) - 26-(2-dimethylaminobutyl)sulphonylpristinamycin IIg

According to the invention, the products of general formula (I) can be prepared by oxidation of a

derivative of pristinamycin II_B, of its salt or of a protected derivative, of general formula:



in which R is defined as above, it being understood that
 5 in the cases where R contains a sulphur-containing hetero cyclic ring, the sulphur atom can be in the form of a sul phide, sulfoxide or sulphone.

The reaction is generally carried out by means of
 an oxidizing agent, optionally prepared in situ, in an
 10 aqueous medium or in an organic solvent, preferably a chlorinated solvent (methylene chloride, 1,2-dichloro- ethane or chloroform, for example) or an alcohol (methanol or tert-butanol, for example) or a mixture of these sol- vents. Optionally the operation can be carried out under
 15 nitrogen.

Among the oxidizing agents which are suitable for preparing a product of general formula (I) in which
 $n = 1$, it is possible to mention organic peracids: per-
 carboxylic or persulphonic acids (for example peracetic,
 20 pertrifluoroacetic, performic, perbenzoic, m-chloroper- benzoic, p-nitroperbenzoic, permaleic, monoperphthalic, percamphoric or p-toluenepersulphonic acids). or inorganic

25

peracids (for example periodic or persulphuric acid).

When the intention is to prepare a product of general formula (I) in which $n = 2$, the operation is advantageously carried out in the presence of selenium dioxide and hydrogen peroxide, using the salt of the product of general formula (II), or in the presence of a peracid such as those referred to above, especially pertrifluoroacetic acid, or m-chloroperbenzoic acid.

When the derivative of pristinamycin II_B of general formula (II) is used in the form of a salt, use is made of the salts formed with organic or inorganic acids, preferably with trifluoroacetic, tartaric, acetic, benzoic or hydrochloric acids.

When the product of general formula (II) is used in the form of a salt or of a protected derivative, the reaction is advantageously carried out at a temperature between ³¹-40 and ³¹50°C.

When it is intended to prepare a product of general formula (I) in which $n = 1$, it is also advantageous to operate by starting from the derivative of pristinamycin II_B of general formula (II) in the presence of an alkali metal bicarbonate (for example sodium bicarbonate) at a temperature between ³¹-60 and ³¹-40°C.

When R contains an alkylamino or cycloalkylamino substituent, it is also possible to utilize a protected derivative of the product of general formula (II). The latter can be protected by any amine-protective group

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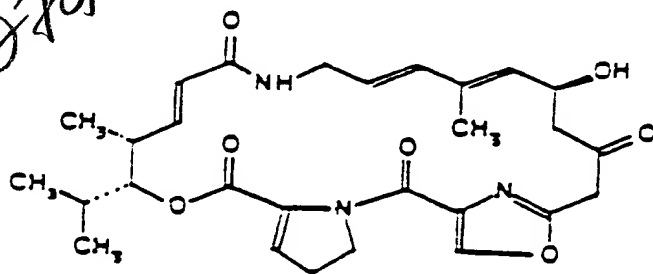
whose introduction and removal do not affect the remainder of the molecule; use is advantageously made of the trifluoroacetyl group which can be removed after the reaction by treatment with an alkali metal bicarbonate (sodium or potassium bicarbonate) in an aqueous solution.

The products of general formula (II) can be prepared by the reaction of a product of general formula:

R-H

(III)

in which R is defined as above, with the product of formula:



(IV)

that is to say pristinamycin II_A.

The reaction is usually carried out in an organic solvent such as an alcohol such as methanol or ethanol, or a chlorinated solvent such as methylene chloride, 1,2-dichloroethane or chloroform, or in a mixture of these solvents (for example methylene chloride/methanol) at a temperature between -30 and 50°C.

Occasionally it may be advantageous to operate in the presence of a tertiary amine, for example triethylamine, or of an ethanolamine (for example dimethylethanolamine),

RTB

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A person skilled in the art will understand that, when R denotes a radical containing a secondary amine group capable of interfering with the reaction, this group will need to be protected beforehand, before the product of general formula (III) is reacted with the product of formula (IV). Any usual means which enables a secondary amine function to be blocked in the form of a labile radical can be used for this purpose. It is especially advantageous to use the trifluoroacetyl radical as a blocking radical which can be removed as described above. In such a case, however, it is not absolutely essential to remove the protective radical, and the protected derivative can be used directly in the oxidation reaction.

According to the invention, the products of general formula (I) in which n is equal to 2 can also be prepared by the oxidation of a product of general formula (I) in which n is equal to 1.

The reaction is carried out under conditions which are similar to the conditions described above for preparing a product of general formula (I) in which $n = 2$ starting from a pristinamycin II_B derivative of general formula (II).

The new products of general formula (I) can be purified by known methods, for example by crystallization, chromatography or successive extractions in an acidic or basic medium. For the person skilled in the art who is



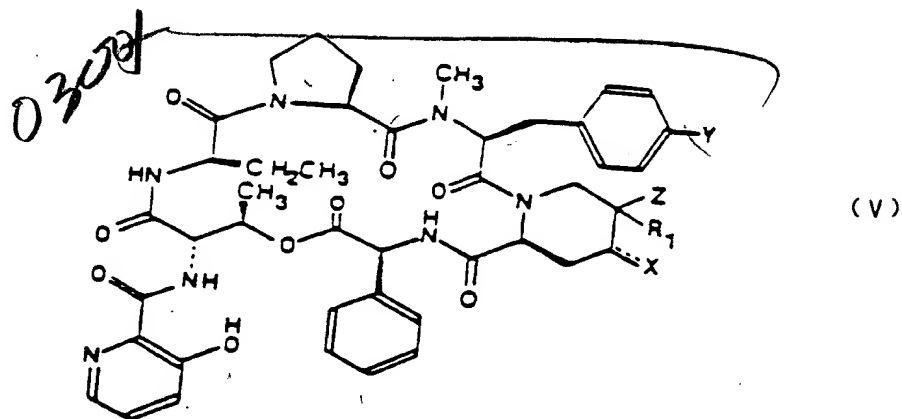
aware of the sensitivity of synergistins in an alkaline medium, a "basic medium" is understood to mean a medium which is just alkaline enough to liberate the parent substance from its salt of addition with an acid, that is to say a medium whose pH does not exceed 8.

It is well known that the synergistins obtained by fermentation constitute products which are greatly sought after by medical practitioners for the treatment of many complaints due to Gram-positive bacteria (of the Staphylococci, Streptococci, pneumococci or enterococci type) and Gram-negative bacteria (of the Haemophilus, gonococci, meningococci type). However, these products have the disadvantage of being insoluble in an aqueous medium and consequently can be administered only by oral route, generally in the form of gelatine capsules, coated pills or tablets. In view of this insolubility, it has hitherto been impossible to use the known synergistins when the patient is unable to swallow; this is the case, in particular, in paediatrics and in reanimation, while the activity spectrum of these products would render them a valuable indication in many circumstances, for example in cases of comatose septicaemias.

The new products according to the invention have the considerable advantage of being capable of being dissolved in water, usually in the form of salts, in usable therapeutic doses, and of enhancing, via a synergism phenomenon, the antibacterial action of pristinamycin 1A,

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virginiamycin S or of derivatives of soluble synergists of general formula:



5 in which Y denotes a hydrogen atom or a dimethylamino radical and

Po 1) either --- denotes a single bond, Z and R₁ denote a hydrogen atom and X denotes a radical of general formula:



10x10
Ri in which:

15 either R₂ denotes a hydrogen atom and R₃ denotes a hydroxy or alkyl radical optionally substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-membered hetero-cyclic ring chosen from azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl or azepinyl rings, or R₃ denotes a cycloalkyl radical containing 3 to 7 carbon atoms

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or a saturated 4 to 7-membered heterocyclic ring chosen
5 from the azetidine, pyrrolidine, piperidine and azepine
rings, these heterocyclic rings being optionally capable
of being substituted by an alkyl radical on the nitrogen
atom,

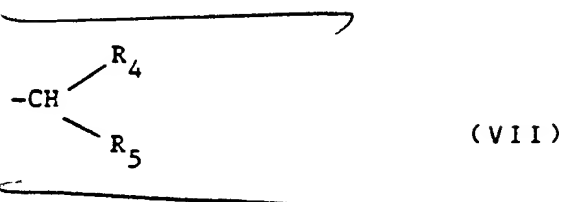
10 ~~or~~ R₂ denotes a formyl or alkylcarbonyl radical and R₃
denotes an alkyl radical substituted by a carboxy, alkyl-
amino or dialkylamino radical whose alkyl radicals can
form, with the nitrogen atom to which they are attached a 4,
to 7-membered heterocyclic ring chosen from azetidinyll,
pyrrolidinyll, piperidinyll, piperazinyll, N-alkylpiperazinyll
15 or azepinyll ring, or R₃ denotes a 4 to 7-membered hetero-
cyclic ring chosen from the azetidine, pyrrolidine, pipe-
ridine and azepine rings, these heterocyclic rings being
capable of being substituted by an alkyl radical on the
nitrogen atom,

20 ~~or~~ R₂ and R₃, which are identical or different, denote an
alkyl radical optionally substituted by a carboxy, alkyl-
oxycarbonyl, hydroxy, alkylamino or dialkylamino radical
whose alkyl radicals optionally form, with the nitrogen
atom to which they are attached, a 4 to 7-membered hetero-
25 cyclic ring chosen from azetidinyll, pyrrolidinyll, piperi-
dinyll, piperazinyll, N-alkylpiperazinyll or azepinyll

30 ~~or~~ R₂ and R₃ form, together with the nitrogen atom to
which they are attached, a 4 to 7-membered heterocyclic
ring chosen from the azetidine, pyrrolidine, piperidine,
morpholine and piperazine rings, optionally substituted

by an alkyl radical,

2) or --- denotes a double bond, X denotes an oxygen atom and Z denotes a radical of general formula:



defined as follows:

(a) either R₁ and R₅ each denote a hydrogen atom and R₄ denotes a 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical) or R₄ denotes an alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino, or dialkylamino (optionally substituted by a mercapto or dialkylamino radical) radicals, or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical) morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl and 2- or 3-pyrrolidinyl radicals (the latter two rings being optionally substituted by an alkyl radical on the nitrogen atom),

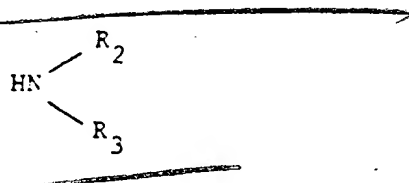
(b) or R₁ and R₅ together form a valency bond and R₄ denotes a 3-pyrrolidinylamino, 3- or 4-piperidylamino, 3-pyrrolidinylloxy, 3- or 4-piperidylloxy, 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical on the nitrogen atom in the ring), or R₄ denotes an alkylamino,

alkyloxy or alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino, dialkylamino (optionally substituted by a dialkylamino radical), trialkylammonio or 4- or 5-imidazolyl radicals or by one or two rings
 5 chosen from piperazino (optionally substituted by an alkyl or mercapto alkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidinyl and 2- or 3-pyrrolidinyl radical (the last two rings being optionally substituted by an alkyl radical on the nitrogen
 10 atom), it being understood that the alkyl radicals and alkyl moieties referring to the symbols of the general formula (V) contain 1 to 5 carbon atoms and form a linear or branched chain.

Some of the derivatives of synergistins of general
 15 formula (V) can have isomeric forms. It is to be understood that these isomeric forms as well as their mixtures can be advantageously associated with the products of general formula (I).

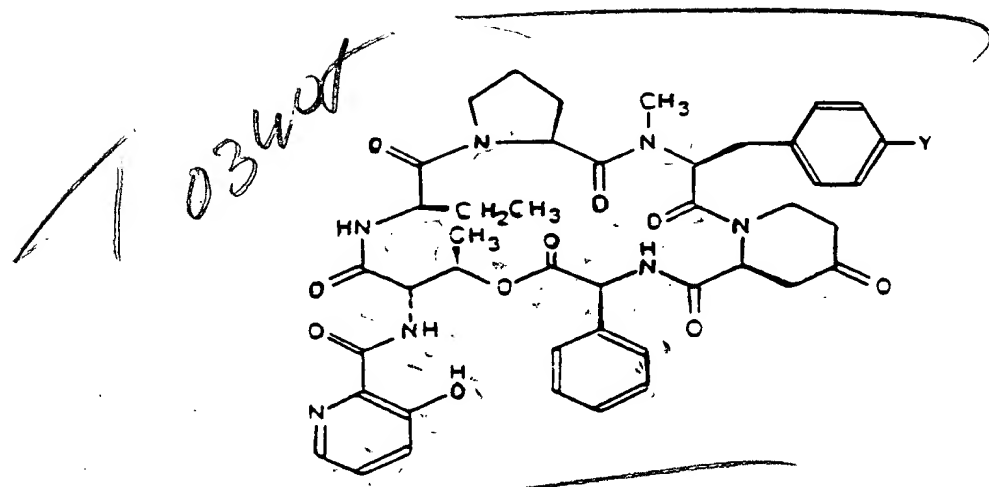
The products of general formula (V) defined as
 20 above under 1), with the exception of those in which R₂ denotes a formyl or alkylcarbonyl radical, can be prepared by the action of an amine of general formula:

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(VIII)

in which R₂ and R₃ are defined as above, on a synergistin
 25 of general formula:



in which Y denotes a hydrogen atom (virginiamycin S) or the dimethylamino radical (pristinamycin I_A), in the presence of an alkali metal cyanoborohydride.

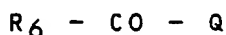
- 5 The operation is generally carried out with an excess of amine of general formula (VIII) in the presence of an alkali metal cyanoborohydride such as sodium cyanoborohydride, in an organic solvent such as an alcohol containing dissolved gaseous hydrogen chloride (methanolic hydrogen chloride or ethanolic hydrogen chloride) at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

The reaction can be advantageously carried out in the presence of a drying agent such as molecular sieves.

The products of general formula (V) defined as above under 1) in which R² denotes a formyl or alkylcarbonyl radical and R₃ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals optionally form, with the nitrogen atom to

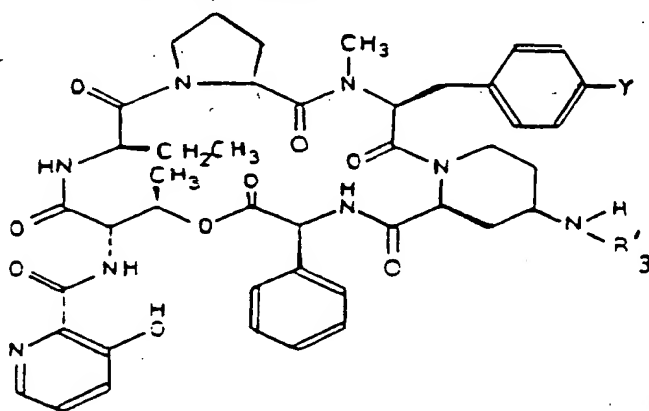
which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidiny, pyrrolidiny, piperidiny, piperaziny, alkyl-piperaziny or azepiny ring, or denotes a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being capable of being substituted by an alkyl radical on the nitrogen atom, and Y is defined as above, can be prepared by the action of a product of general formula:

10



(X)

in which R_6 denotes a hydrogen atom or an alkyl radical and Q denotes a halogen atom or an alkylcarbonyloxy radical, on a product of general formula:



(XI)

15 in which Y is defined as before and R'_3 has the corresponding definition of R_3 which is given above.

The reaction is usually carried out in an organic solvent such as pyridine, in a chlorinated solvent (methylene chloride) or an ether (tetrahydrofuran) in the presence

of an acid acceptor such as an organic base such as triethylamine or an inorganic base such as an alkali metal carbonate or bicarbonate such as sodium bicarbonate, the operation being carried out at a temperature between 0 and 80°C.

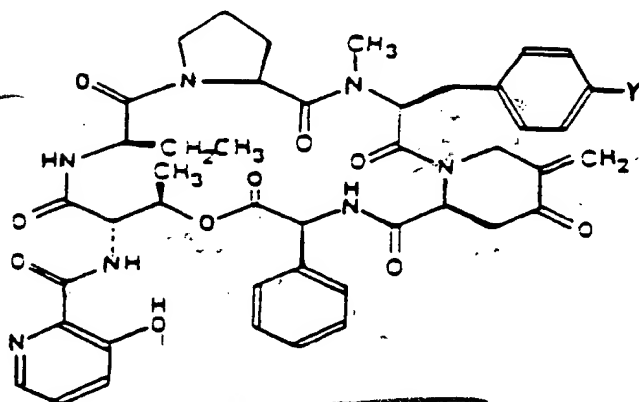
It is to be understood that, when R'_3 denotes a radical containing a secondary amine group, the said group must be protected before the product of general formula (X) is reacted with the product of general formula (XI). The protection is carried out under the conditions described earlier for the preparation of the product of the general formula (II).

It is also to be understood that, when R_2 and/or R_3 in the general formula (VIII) denote a radical containing a secondary amine group, the latter must be protected beforehand, before the product of general formula (VIII) is reacted with the product of general formula (IX). The blocking and the deblocking are carried out as described earlier.

The products of general formula (V) defined as before under (2), in which Y is defined as before and the other symbols are defined as before under (2) a) can be prepared by the action of a product of general formula:

R'_4-H (XII) R_5
in which R'_4 has the definition of R_4 given earlier under (2) a), on the product of general formula:

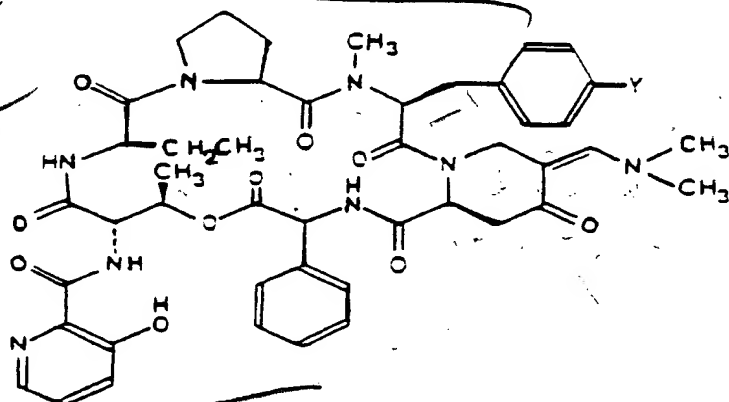
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B in which Y is defined as before.

P The operation is usually carried out in an organic solvent such as an alcohol such as methanol, or a chlorinated solvent such as chloroform, or a mixture of these solvents, at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

The products of general formula (XIII) can be prepared by the action of an alkali metal borohydride such as sodium cyanoborohydride on a product of general formula:



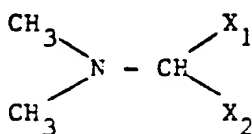
B in which Y is defined as before.

15 P The operation is usually carried out in an organic

solvent such as an ether such as tetrahydrofuran, or an alcohol, for example isopropanol, in the presence of an acid such as trifluoroacetic acid, at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of

5 20°C.

The products of general formula (XIV) can be obtained by the action of a product of formula:



(XV)

in which either X₁ denotes an alkyloxy radical and X₂ denotes an alkyloxy or dimethylamino radical, or X₁ and X₂ both denote a dimethylamino radical, on a product of general formula (IX).

In practice, it is advantageous to react tert-butoxybis(dimethylamino)methane with the product of general formula (IX), the operation being carried out in an organic solvent such as a chlorinated solvent such as 1,2-dichloroethane, or an amide (for example dimethylformamide) at a temperature between 0 and 80°C, preferably at a temperature in the region of 20°C.

20 The products of general formula (XV) can be prepared according to the methods described by H. Brederick et al., Chem. Ber., 101, 41 and 3058 (1968) and Chem. Ber., 106, 3725 (1973).

The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) b), except for R_4 denoting a 3-pyrrolidinyloxy, 3- or 4-piperidyloxy or alkyloxy radical, optionally substituted as defined under 2) b), can be prepared by the action of a product of general formula:



in which R''_4 has the definition of R_4 given above, on a product of general formula (XIV) in which Y is defined as earlier.

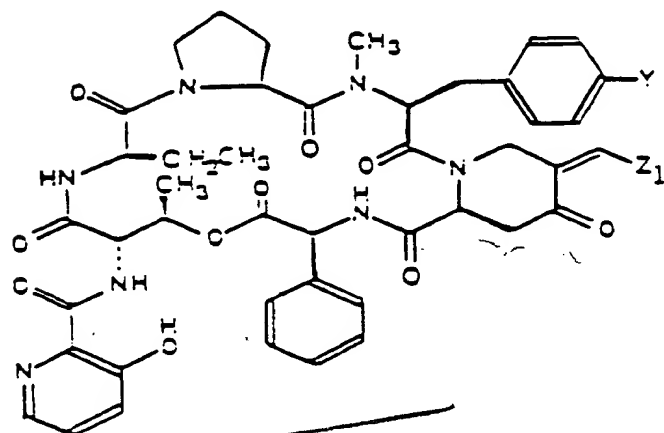
The reaction is carried out in an organic medium in the presence of an acid (for example acetic acid or a mixture of acetic acid with catalytic quantities of trifluoroacetic acid), in the presence or absence of a solvent, at a temperature between 0 and 50°C; preferably at a temperature in the region of 20°C.

Where applicable, the solvent can be chosen from organic solvents such as ethers (tetrahydrofuran), alcohols (ethanol) and chlorinated solvents (methylene chloride or chloroform, for example).

The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) b) can be prepared by the action of a product of general formula:



in which R'''_4 is defined as R_4 under 2) b), on a product of general formula:



(XVIII)

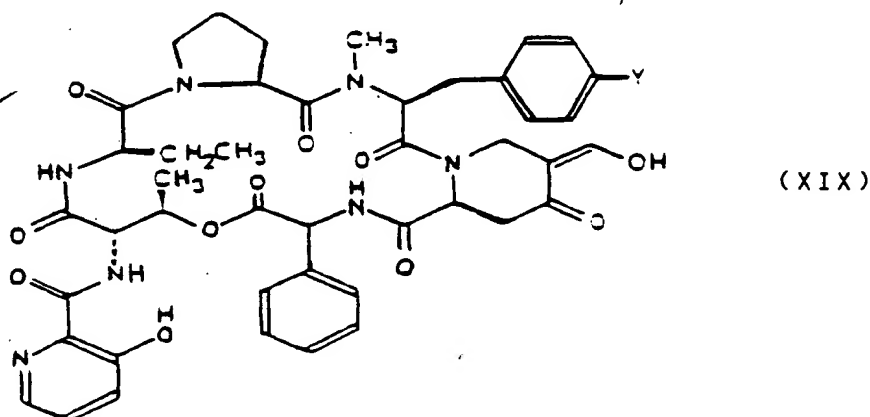
in which Y is defined as before and Z₁ denotes a tosyloxy, acetyloxy, trimethylsilyloxy or dialkyloxyphosphoryloxy radical whose alkyl moieties contain 1 to 4 carbon atoms forming a linear or branched chain or Z₁ denotes a chlorine atom.

The operation is usually carried out in an organic solvent such as an ether such as tetrahydrofuran, an alcohol such as ethanol, or a chlorinated solvent (methylene chloride or chloroform, for example) at a temperature in the region of 20°C. The reaction is carried out in a basic medium, for example in the presence of an alkali metal hydride or an alkali metal alcoholate such as sodium ethoxide or potassium tert-butoxide.

When R''₄ is different from a substituted alkyloxy or (heterocyclic ring radical)oxy radical, it is also possible to operate either in a neutral medium at a temperature between 0 and 50°C, in one of the solvents mentioned above, or in an acetic medium under conditions identical to those described earlier for the action of a

product of general formula (XVI) on a product of general formula (XIV).

The products of general formula (XVIII) can be prepared by acid hydrolysis of a product of general formula (XIV) to obtain a product of general formula:



followed:

(A) either by the action of a product of general formula: Z_1-X (XX) in which X denotes a halogen atom and Z_1 has the definition given before for Z_1 , except for denoting a chlorine atom

(B) or by the action of a product of formula: $(C_6H_5)_3 P Cl_2$ (XXI)

to obtain a product of general formula (XVIII) in which Z_1 denotes a chlorine atom.

The hydrolysis of the product of general formula (XIV) to the product of general formula (XVIII) is carried out by means of an aqueous solution of an inorganic acid such as a 0.1 N aqueous solution of hydrochloric acid, the

operation being carried out at a temperature in the region of 20°C.

B The reaction of the product of general formula (XX) with the product of general formula (XIX) is generally carried out in an organic solvent such as methylene chloride in the presence of an acid-acceptor such as an organic base such as triethylamine, or an inorganic base such as an alkali metal carbonate or bicarbonate, for example sodium or potassium bicarbonate. The operation is generally carried out at a temperature between -20 and +20°C.

P The reaction of the product of general formula (XXI) with the product of general formula (XIX) is usually carried out in a chlorinated solvent such as methylene chloride at a temperature between -20 and +20°C.

15 The products of general formulae (III), (VIII), (XII), (XVI) and (XVII) can be prepared according to, or in a similar manner to, the methods described in the examples below, and especially according to:

- G.G. Urquart et al., Org. Synth., 21, 36 (1941)
- 20 - A.I. Vogel, J. Chem. Soc., 1822 (1948)
- J.H. Chapman and L.N. Owen, J. Chem. Soc., 579 (1950)
- H.R. Snyder et al., J. Am. Chem. Soc., 69, 2672 (1947)
- D.D. Reynolds et al., J. Org. Chem., 26, 5125 (1961)
- J.W. Haeffele et al., Proc. Sci. Toilet Goods Assoc., 32, 52 (1959)

Po H. Barrer et al., J. Org. Chem., 27, 641 (1962)

W

J.H. Biel et al., J. Amer. Chem. Soc., 77, 2250 (1955)
when dealing with a product of general formula (III),
(XII), (XVI) or (XVII) in which R, R'₄, R''₄ or R'''₄
denotes a substituted alkylthio or (heterocyclic ring

5 radical)thio radical, or according to:

A.J.W. Headlee et al., J. Amer. Chem. Soc., 55, 1066
(1933)

B.K. Campbell and K.N. Campbell, J. Amer. Chem. Soc.,
10 60, 1372 (1938)

R.C. Elderfield et al., J. Amer. Chem. Soc., 68, 1579
(1946)

when dealing with a product of general formula (XVI) or
(XVII) in which R''₄ or R'''₄ denotes a substituted
15 alkyloxy or (heterocyclic ring radical)oxy radical, or
according to:

J. Amer. Chem. Soc., 54, 1499 (1932) and

J. Amer. Chem. Soc., 54, 3441 (1932),

when dealing with a product of general formula (VIII) or
20 of general formula (III), (XVI) or (XVII) in which R, R''₄
or R'''₄ are substituted alkylamino radicals, or accor-
ding to:

E.F. Elslager et al., J. Med. Chem., 17, 99 (1974)

L.M. Werbel et al., J. Het. Chem., 10, 363 (1973)

25 when dealing with a product of general formula (III),
(XVI) or (XVII) in which R, R''₄ or R'''₄ are (hetero-
cyclic ring radical)amino radicals.

It is to be understood that in the above methods,

when R , R_2 , R_3 , R'_4 , R''_4 or R'''_4 contain a secondary amine group capable of interfering with the reaction, this must first be protected by any known method which does not affect the remainder of the molecule. The protective
5 radical is removed after reaction under the conditions described earlier.

Where applicable, the isomers of the products of general formula (I) and/or of the products of general formula (V) can be separated by chromatography or by high
10 performance liquid chromatography.

The products of general formula (V) can be purified as mentioned earlier for the products of general formula (I).

The pristinamycin II_B derivatives of formula (I) and
15 their pharmaceutically acceptable salts exhibit particularly advantageous antibacterial properties in vitro and in vivo.

In vitro, the products of formula (I) have shown themselves to be active towards Staphylococcus aureus Smith at concentrations from 4 to 100 $\mu\text{g}/\text{cm}^3$. In addition, they
20 have a synergistic effect on the antibacterial action of pristinamycin I_A in concentrations greater than 0.1 and 10 $\mu\text{g}/\text{cm}^3$.

In vivo, the products of formula (I) have shown themselves to be active in the mouse in experimental infections
25 with Staphylococcus aureus Smith at dosages between 40 mg/kg and dosages greater than 300 mg/kg by the

44

subcutaneous route. When they are combined with pristina-mycin I_A in proportions from 10-90% to 90-10%, they have a synergistic effect on the antimicrobial action at dosages between 8 and 200 mg/kg by the subcutaneous route.

5 The acute toxicity of the products of formula (I), expressed as their LD₅₀, is generally between 300 mg/kg and dosages greater than 1 g/kg by the subcutaneous route in the mouse.

 The products of special interest are those of
10 formula (I) in which the symbol R denotes:
- either a nitrogen-containing 5 or 6-membered heterocyclic ring radical unsubstituted or substituted by an alkyl radical,
- or an alkyl chain of 2 to 4 carbon atoms and substituted
15 by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, and N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino, dialkylcarbamoyloxy (the alkyl moieties of these two latter radicals being unjoined or joined to form, with the nitrogen atom to which
20 they are attached, a saturated or unsaturated 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl), or substituted by a nitrogen-
25 containing 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone and

unsubstituted or substituted by alkyl, this heterocyclic ring being linked to the alkyl by a carbon atom of the ring, it being understood that a least one of the substituents carried by the above alkyl chain is a nitrogen-containing substituent capable of forming salts, and n is 1 or 2 ;

5 and, among these products, those which are especially active are the products of formula (I) in which R denotes an alkyl chain containing 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 to 6 ring atoms, N -alkyl- N -cycloalkylamino of 5 or 6

10 ring atoms, alkylamino of 1 to 4 carbon atoms, and dialkylamino (in which the alkyl moieties contain 1 to 3 carbon atoms each or form, with the nitrogen atom to which they are attached, a saturated 5 or 6-membered heterocyclic ring), or R denotes a nitrogen-containing 5 or 6-membered

15 heterocyclic ring unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the alkyl chain being a nitrogen-containing substituent capable of forming salts, and at least one of the radicals carried by this chain is placed in a 1- or

20 2- position, and n is 1 or 2.

The following derivatives of pristinamycin II_B of formula (I) are of especial interest.

- 26-(2-diethylamino-1-methylethyl)sulphinylpristinamycin

IIb

- 26-[(2R)2-dimethylaminobutyl]sulphinylpristinamycin IIb

- 26-(2-diethylaminopropyl)sulphinylpristinamycin IIb

5 - 26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIb.

For use in therapy, the compounds of formula (I) can be used as such, that is to say in the form of the base, in combination with already known synergists, but, since the chief advantage of the products of the invention is
10 their solubility in water, it is especially advantageous to use them in the form of pharmaceutically acceptable salts, in combination with known synergists or with the synergists of formula (V), dissolved either in the form of pharmaceutically acceptable salts or, where applicable, in
15 the form of the base when the solubility is sufficient for the solution produced to contain (in a volume suitable for a single dose) a quantity of active ingredient which is at least equal to the therapeutically active dose.

Both for the products of formula (I) and for the
20 products of formula (V), the pharmaceutically acceptable salts which can be mentioned are the salts of addition with inorganic acids such as hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, or with organic acids, such as acetates, propionates, succinates, maleates,
25 fumarates, methanesulphonates, p-toluenesulphonates, isethionates, or substitution derivatives of these

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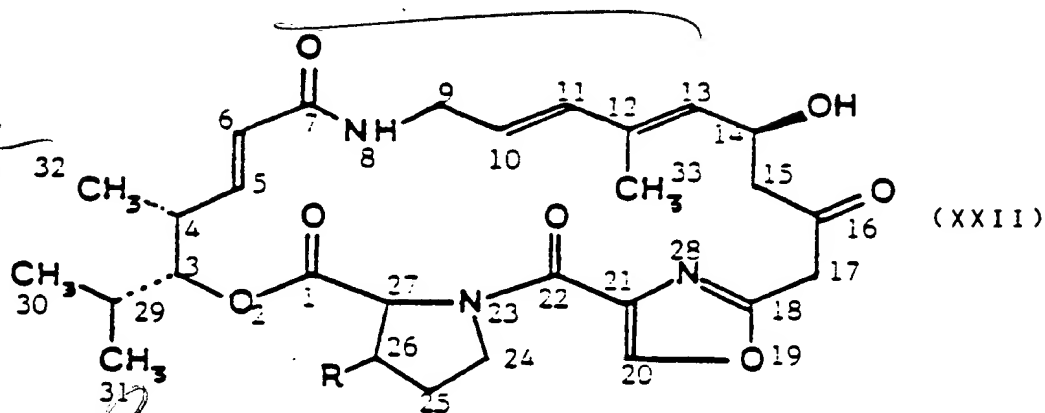
compounds. There can also be mentioned, as pharmaceuti-
cally acceptable salts, the salts with alkali metals (such
as sodium and potassium salts), with alkaline-earth metals
(such as the magnesium salt), the ammonium salt and salts
5 of addition with nitrogen-containing organic bases (etha-
nolamine, diethanolamine, trimethylamine, triethylamine,
methylamine, propylamine, diisopropylamine, N,N-dimethyl-
ethanolamine, benzylamine, dibenzylamine, dicyclohexyl-
benzylamine, N-benzyl- β -phenethylamine, N,N'-dibenzyl-
10 ethylenediamine, benzhydrylamine, arginine, leucine,
lysine or N-methylglucamine).

Quaternary ammonium salts corresponding to the
anions listed above can be mentioned as pharmaceutically
acceptable salts for the products of general formula (V)
15 in which Z denotes a radical of general formula (VII) in
which R₄ denotes a trialkylammonio radical.

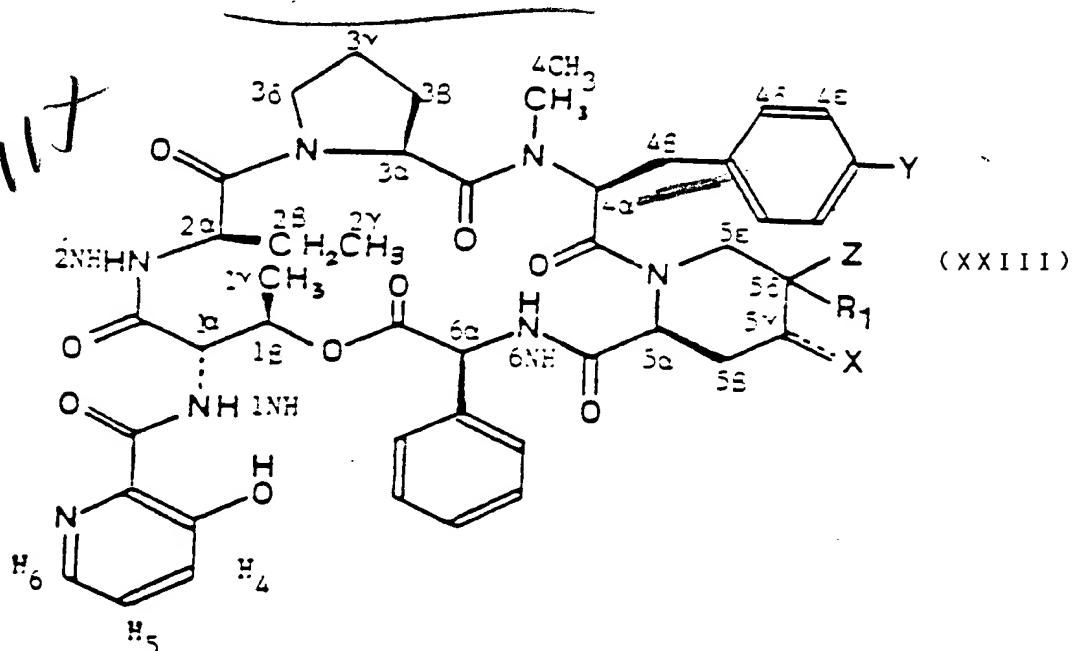
The following examples, given without implying
any limitation, show how the invention can be put into
practice. The NMR spectra of the products illustrated in
20 these examples and in the reference examples which follow,
show general characteristics which are common to all the
products of general formula (I) or of general formula (V)
and individual characteristics which are specific to each
of the products, depending on the substituents. Only the
25 individual characteristics due to the changeable radicals
are mentioned in the examples or reference examples which
follow. For the products of general formula (I), all the

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protons are designated according to the numbering indicated in the following formula:



For the synergists of general formula (V) all the protons are designated according to the numbering indicated in the general formula (XXIII); this numbering is that recommended by J.O. Anteunis et al., [Eur. J. Biochem., 58, 259 (1975)].



Unless stated otherwise, all the spectra were recorded at 250 MHz in deuteriochloroform; the chemical shifts are expressed in ppm relative to the tetramethylsilane signal. The abbreviations used in the following text are as follows:

s = singlet
d = doublet
t = triplet
mt = multiplet
m = unresolved bands
dd = doublet of doublets
dt = doublet of triplets
ddd = doublet of doublets of doublets
dddd = doublet of doublets of doublets of doublets

It is to be understood that the various isomers have been classified arbitrarily according to the chemical shifts observed in NMR.

The names isomer A₁ and isomer A₂ of the products of general formula (I) in which n = 1 are given to the isomers which have the characteristics:

approximately 1.7 (s, -CH₃ at 33); approximately 3.8 (s, >CH₂ at 17); < 5 (d, -H₂₇) isomer A₂ or > 5 (d, -H₂₇) isomer A₁; approximately 5.50 (broad d, -H₁₃); approximately 6.20 (d, -H₁₁); approximately 6.6 (>NH at 8); > 8 (s, -H₂₀).

The names isomer B₁ and isomer B₂ of the products of general formula (I) in which n = 1 are given to

the isomers which have the characteristics:
approximately 1.5 (s, -CH₃ at 33); approximately 3.7 and
3.9 (2d, >CH₂ at 17); approximately 4.8 (mt, -H₁₃);
< 5 (d, -H₂₇) isomer B₂ or > 5 (d, -H₂₇) isomer B₁;
5 approximately 5.70 (borderline AB, -H₁₁ and -H₁₀); approxi-
mately 7.7 (>NH at 8); approximately 7.8 (s, -H₂₀).

The name isomer A of the product of general for-
mula (II) is given to the isomer which has NMR characteris-
tics identical to those listed above for the isomers A₁
10 and A₂ of the products of general formula (I), it being
understood that the H at 27 is characterized by: 4.7 (d,
J ≤ 1 Hz).

20 The name isomer B of the product of general formula
(II) is given to the isomer which has NMR characteristics
15 identical to those listed above for the isomers B₁ and
B₂ of the products of general formule (I), it being
understood that the H at 27 is characterized by: 4.6 (d,
J ≥ 2.5 Hz).

In the following examples, the name "flash" chroma-
20 tography is given to a purification technique in which a
short chromatography column is used and operated under an
intermediate pressure (50 kPa) with the use of a silica
with a particle size distribution of 40-53 μm, according to
W.C. Still, M. Kahn and A. Mitra (J. Org. Chem. 43, 2923
25 (1978)).

DEP In the examples described below, unless stated
otherwise, all the products can be dissolved at a strength
of at least 2%, in the form of hydrochloride.

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EXAMPLE 1

Trifluoroacetic acid (0.4 cc), and then 85% meta-chlorobenzoic acid (1.06 g) are added, under a nitrogen atmosphere, while the temperature is maintained at 0°C, to 26-(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer A) (3.59 g) dissolved in dichloromethane (40 cc) at 0°C. After 20 hours' stirring at 25°C, the reaction mixture is added to a saturated aqueous solution of sodium bicarbonate. The organic phase is separated off and then the aqueous phase is washed with methylene chloride (3 x 100 cc). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give a yellow solid (4.2 g) which is purified by "flash" chromatography [(eluent: chloroform-methanol (90-10 by volume)], 20-cc fractions being collected. Fractions 22 to 28 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give a light-yellow solid, which is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinypristinamycin II_B (isomer A₂) (0.62 g) in the form of a yellow powder melting at about 155°C.

NMR spectrum:

0.90 to 1.15 [mt, -CH₃ at 32, 31, 30, $\text{>N}(\text{CH}(\text{CH}_3)_2)_2$]

1.76 (s, -CH₃ at 33)

2.75 to 3.15 (mt, >CH₂ at 15, -H₄ and $\begin{array}{c} \text{CH-} \\ \downarrow \\ \text{-S-CH}_2\text{-CH}_2\text{N} \\ \downarrow \quad \quad \quad \downarrow \\ \text{O} \quad \quad \quad \text{CH-} \end{array}$)

3.81 (s, >CH₂ at 17)

5 4.76 (d, -H₂₇)

5.51 (d, -H₁₃)

6.20 (d, -H₁₁)

6.48 (m, >NH at 8)

8.13 (s, -H₂₀)

10 *P* Fractions 35 to 45 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give a light-yellow solid which is stirred in ethyl ether (15 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinyl-
15 pristinamycin II_B (80% isomer A₁, 20% isomer A₂) (1.07 g) in the form of a light-yellow powder melting at about 145°C.

P NMR spectrum (isomer A₁):

1.72 (s, -CH₃ at 33)

20 2.70 to 3.15 (mt, >CH₂ at 15, -H₄, $\begin{array}{c} \text{-S-CH}_2\text{-CH}_2\text{-N-CH} \\ \downarrow \quad \quad \quad \downarrow \\ \text{O} \quad \quad \quad \text{CH} \end{array}$)

3.81 (s, >CH₂ at 17)

5.26 (d, -H₂₇)

5.46 (d, -H₁₃)

25 6.15 (d, -H₁₁)

8.11 (s, -H₂₀)

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26-(2-Diisopropylaminoethyl)thiopristinamycin II_B
can be prepared as follows:

2-Diisopropylaminoethanethiol (16 g) dissolved in
dichloromethane (30 cc) is added dropwise under a nitrogen
5 atmosphere to pristinamycin II_A (52 g) dissolved in a
mixture of dichloromethane (260 cc) and methanol (520 cc),
at -30°C. The solution is stirred at -20°C for 20
hours and then concentrated under reduced pressure (2.7
kPa) at 30°C. The solid obtained is stirred with ethyl
10 ether (2 x 1000 cc), separated off by filtration and then
crystallized from acetonitrile (100 cc). The crystals
are separated off by filtration and then dried under
reduced pressure (90 Pa) at 40°C. In this manner, 26-
(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer
15 A) (33.6 g) is obtained in the form of white crystals melt-
ing at about 122°C.

NMR spectrum:

1 to 1.15 (mt, isopropyl-CH₃)

1.72 (s, -CH₃ at 33)

20 1.80 to 2.20 (mt, -H₂₅, -H₂₉)

2.50 to 3 (mt, -SCH₂CH₂-N $\begin{matrix} \text{CH} \diagup \\ \text{CH} \diagdown \end{matrix}$)

3.40 (broad d, -H₂₆)

25 4.74 (broad s, -H₂₇)

6.32 (m, -NH₈)

8.15 (s, -H₂₀)

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2-Diisopropylaminoethanethiol can be prepared according to the method described by D.D. Reynolds, D.L. Fields and D.L. Johnson, J. Org. Chem. 26, 5125 (1961).

EXAMPLE 2

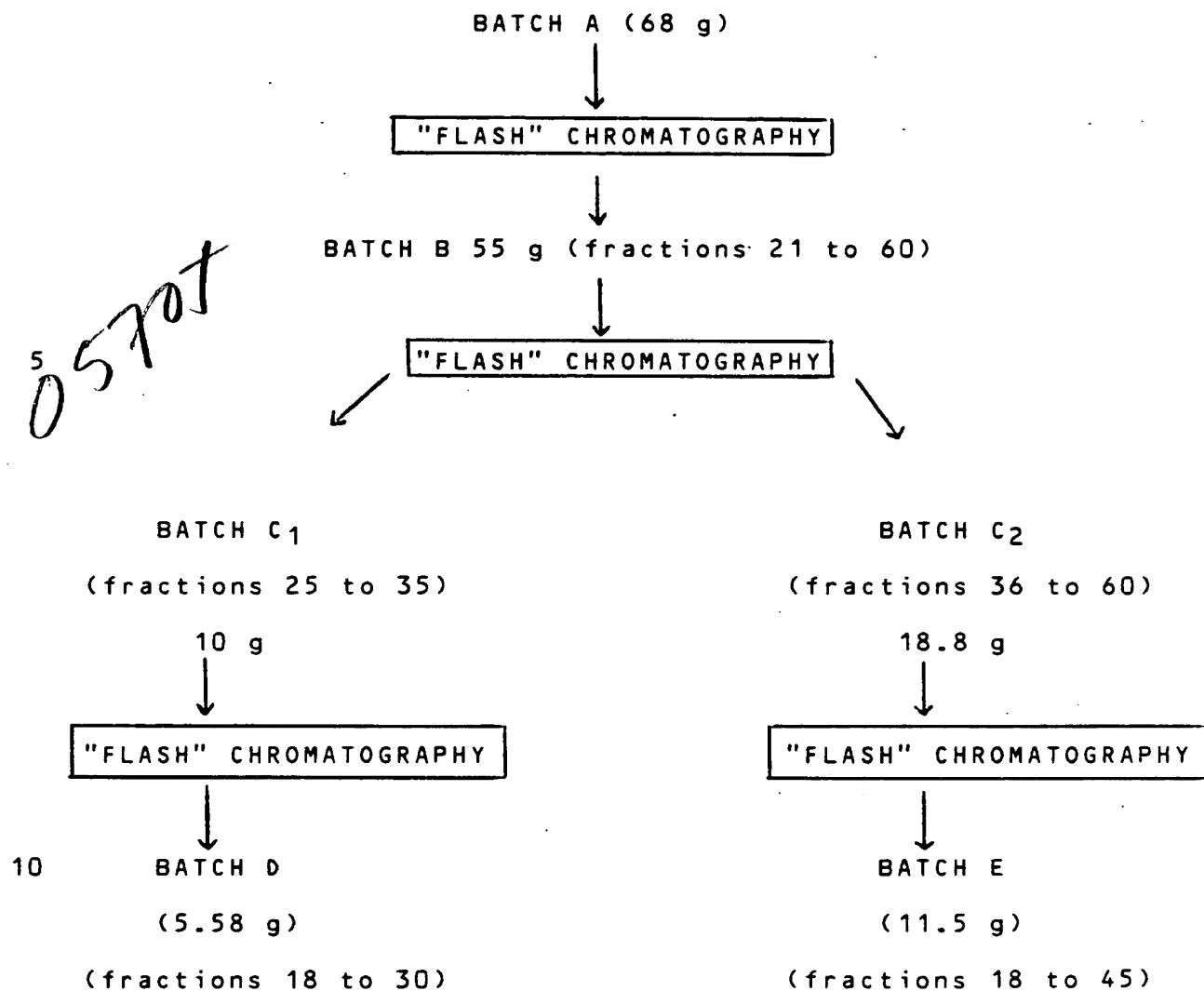
5 Sodium bicarbonate (1.22 g) is added to 26-(2-di-isopropylaminoethyl)thiopristinamycin IIg (isomer A) (10 g) dissolved in chloroform (300 cc). The mixture is cooled to -50°C and 98% meta-chloroperbenzoic acid (2.98 g) dissolved in chloroform (100 cc) is added drop-
10 wise. The mixture is stirred at -50°C for 2 hours 15 minutes and then a saturated aqueous solution of sodium bicarbonate is added to it. After 15 minutes' stirring at 25°C, the mixture is separated and then the aqueous phase is washed with dichloromethane (3 x 200 cc). The
15 organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give a whitish porous solid (10.62 g). The latter is dissolved in ethyl acetate (400 cc) and then treated with a 0.1 N aqueous solution
20 of hydrochloric acid (140 cc). The pH of the aqueous solution is then adjusted to 4.2 by adding a pH 4.2 buffer (400 cc). The aqueous phase is separated off and then the organic phase is washed with pH 4.2 buffer (400 cc). The aqueous phases are combined and washed with ethyl acetate
25 (2 x 150 cc). After separation, the aqueous phase is adjusted to pH 7-8 by adding sodium bicarbonate and is then washed with dichloromethane (3 x 300 cc). The organic

phases are combined and then washed with pH 7.5 buffer
(2 x 200 cc). The aqueous phase is washed with dichloro-
methane (50 cc) and then the organic phases are combined,
dried over magnesium sulphate, filtered and concentrated
5 to dryness under reduced pressure (2.7 kPa) at 30°C, to give
a light-yellow solid (8.04 g), which is stirred in ethyl
ether (100 cc), separated off by filtration and then dried
under reduced pressure (90 Pa) at 40°C. In this manner,
26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIg
10 (isomer A₂) (7.5 g) is obtained in the form of a yellow
powder melting at about 158°C, the NMR characteristics
of which are identical to those in Example 1.

EXAMPLE 3

The method used is that described in Example 1,
15 but starting with 26-(2-diethylaminoethyl)thiopristinamycin
IIg (53.2 g), trifluoroacetic acid (6.25 cc) and meta-
chloroperbenzoic acid (16.4 g). Three successive
purifications by "flash" chromatography are carried out
[eluent: chloroform-methanol (90-10 by volume)], 40-cc
20 fractions being collected, according to the following
scheme:

Purification scheme



P In all cases, the fractions recovered are concentrated to dryness under reduced pressure (2.7 kPa) at

15 30°C.

ap Batch D is stirred in ethyl ether (60 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphonylpristinamycin II_B (isomer A₂)

57-

(5 g) is obtained in the form of a yellow powder melting at about 172°C.

P NMR spectrum:

1.00 to 1.14 (mt, -CH₃ at 32) + chain CH₃)

1.75 (s, -CH₃ at 33)

5

2.55 to 3.20 (mt, >CH₂ at 15, -H₄, -S-CH₂-CH₂-N(CH₂-))

3.82 (s, >CH₂ at 17)

4.81 (d, -H₂₇)

5.51 (d, -H₁₃)

10

6.19 (d, -H₁₁)

6.46 (dd, >NH at 8)

8.13 (s, -H₂₀)

P Batch E is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphonylpristinamycin II_B (60% isomer A₂, 15% isomer A₁, 12% isomer B₁, 13% isomer B₂) (10.9 g) is obtained.

P NMR spectrum:

20

1.00 to 1.14 (mt, -CH₃ at 32 and -N(CH₂CH₃)₂ of A₁ and A₂), *13* *13* *UNS*

1.54 (s, -CH₃ at 33 of B₁ and B₂), *13*

1.68 (s, -CH₃ at 33 of A₁), *13*

1.75 (s, -CH₃ at 33 of A₂), *13*

25

2.65 to 2.95 (mt, -S(O)CH₂CH₂N< and H₄ of A₁), *13* *21*

2.55 to 3.20 (mt, >CH₂ at 15, -H₄ and -S(O)CH₂CH₂N< of A₂), *13* *21* *UNS*

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- 5 3.77 (borderline AB, >CH_2 at 17 of A₁),
3.82 (s, >CH_2 at 17 of A₂),
4.81 (d, -H₂₇ of A₂),
5.24 and 5.25 (2d, -H₂₇ of A₁ and of B₁),
5.41 (d, -H₁₃ of A₁),
5.51 (d, -H₁₃ of A₂),
5.99 and 6. (2d, -H₆ of B₁ and -H₆ of B₂),
6.11 (d, -H₁₁ of A₁),
6.19 (d, -H₁₁ of A₂),
10 6.46 (dd, >NH at 8 of A₂),
6.79 (dd, >NH at 8 of A₁),
7.82 (s, -H₂₀ of B₁ and B₂),
8.12 (s, -H₂₀ of A₁),
8.13 (s, -H₂₀ of A₂)
15 P 26-(2-Diethylaminoethyl)thiopristinamycin II_B

can be prepared as follows:

P A solution of diethylaminoethanethiol (3.7 g) in methylene chloride (15 cc) is added to a suspension of pristinamycin II_A (13.1 g) in methanol (150 cc). The
20 solution obtained is stirred at a temperature of about 20°C for 18 hours and is then poured into distilled water (1500 cc); the mixture obtained is extracted 3 times with methylene chloride (1000 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and
25 then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by

volume)] after fractions 5 to 23 have been concentrated to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-diethylaminoethyl)thiopristinamycin II_B (12.4 g) is obtained in the form of a yellow powder melting at about 105°C.

NMR spectrum:

- 1.05 (m, -N(CH₂CH₃)₂ + -H₃₂)
- 1.70 (s, -H₃₃)
- 1.85 to 2.15 (m, -H₂₅, -H₂₉)
- 2.60 (q, -N(CH₂CH₃)₂)
- 2.75 (s, -S-CH₂CH₂-)
- 2.9 (dd, ABX system, -H₁₅)
- 3.10 (dd, ABX system, -H₁₅)
- 3.40 (ddd, -H₂₆)
- 3.80 (s, -H₁₇)
- 4.75 (d, -H₂₇)
- 5.50 (d, -H₁₃)
- 6.15 (d, -H₁₁)
- 6.60 (broad s, NH at 8)
- 8.10 (s, -H₂₀)

EXAMPLE 4

By using a method similar to that described in Example 1, but starting from 26-(2-dimethylaminoethyl)thiopristinamycin II_B (5.5 g), trifluoroacetic acid (0.67 cc) meta-chloroperbenzoic acid (1.8 g), and after a purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 30-cc fractions being collected,

and concentrating fractions 23 to 40 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-dimethylaminoethyl)sulphinypristinamycin II_B (70% isomer A₂, 15% isomer A₁, 7% isomer B₁, 8% isomer B₂) (0.4 g) is
5 obtained in the form of a yellow powder melting at about 150°C.

np
NMR spectrum (isomer A₂):

1.77 (s, -CH₃ at 33)

2.41 (s, -N(CH₃)₂)

10 2.70 to 3.20 (mt, -SCH₂CH₂N<, >CH₂ at 15
and -H₄)
↓
0

3.82 (s, >CH₂ at 17)

4.84 (mt, -H₃ and -H₂₇)

5.52 (d, -H₁₃)

15 6.19 (d, -H₁₁)

6.42 (m, >NH at 8)

8.14 (s, -H₂₀)

P
26-(2-Dimethylaminoethyl)thiopristinamycin II_B

can be prepared as follows:

20 *P* By using a method similar to that described in Example 3, but starting from pristinamycin II_A (2.7 g) and 2-dimethylaminoethanethiol (0.58 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions
25 11 to 17 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-dimethylaminoethyl)thiopristinamycin II_B (1.1 g) is obtained in the form of a yellow powder melting

at about 100°C.

NMR spectrum:

2.35 (s, 6H : $\text{-N(CH}_3\text{)}_2$),
2.80 (m, 4H : $\text{-S-CH}_2\text{CH}_2\text{-N<}$),
3.40 (ddd, 1H : -H_{26}),
4.75 (d, 1H : -H_{27}),
8.10 (s, 1H : -H_{20}).

EXAMPLE 5

By using the same method as that described in Example 2, but starting from 26-(2-N-methyl-N-ethylamino-ethyl)thiopristinamycin IIg (90% isomer A, 10% isomer B) (4.7 g), sodium bicarbonate (1.22 g), and 98% meta-chloro-perbenzoic acid (1.41 g), and after purification by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 44 to 52 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (2.47 g) is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40°C. In this manner, 2-(N-methyl-N-ethyl-2-aminoethyl)sulphinypristinamycin IIg (isomer A₂) (2.3 g) is obtained in the form of a yellow powder melting at about 145°C.

NMR spectrum

1.09 (t, $\text{>N-CH}_2\text{-CH}_3$)
1.76 (s, -CH_3 at 33)
2.31 (s, >N-CH_3)

2.54 (mt, $\text{>N-CH}_2\text{CH}_3$)

2.80 (mt, $-\text{H}_4$)

2.70 to 3.10 (mt, $-\text{S}-\text{CH}_2-\text{CH}_2\text{N}<$)
 \downarrow
O

5 2.92 to 3.12 (2dd, >CH_2 at 15)

3.24 (mt, $-\text{H}_{26}$)

3.82 (s, >CH_2 at 17)

4.82 (s, $-\text{H}_{27}$)

5.51 (d, $-\text{H}_{13}$)

10 6.40 (dd, >NH at 8)

8.13 (s, $-\text{H}_{20}$)

P 26-(N-Methyl-N-ethyl-2-aminoethyl)thiopristinamycin IIg (90% isomer A, 10% isomer B) can be prepared by using the same procedure as that described in Example 1, but starting from pristinamycin IIA (14.11 g) and N-methyl-N-ethyl-2-aminoethanethiol (3.2 g). After stirring for 4 days at -20°C and purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 80-cc fractions being collected, followed by concentration of fractions 25 to 48 to dryness under reduced pressure (2.7 kPa) at 30°C , a yellow solid (4.75 g) is obtained, which is dried under reduced pressure (90 kPa) at 40°C . In this manner, 26-(N-methyl-N-ethyl-2-aminoethyl)thiopristinamycin IIg (90% isomer A, 10% isomer B) (4.7 g) is obtained in the form of a yellow powder melting at about 140°C .

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20

20

NMR spectrum:

- 5 1.1 (mt, CH_2CH_3),
 1.73 (s, CH_3 at 33),
 2.30 (s, $>\text{N}-\text{CH}_3$),
 2.45 to 2.6 (mt, $>\text{N}-\text{CH}_2\text{CH}_3$),
 2.68 to 2.78 (2mt, $-\text{S}-\text{CH}_2-\text{CH}_2\text{N}<$),
 2.78 (mt, $-\text{H}_4$),
 2.90 and 3.12 (2dd, $-\text{CH}_2-$ at 15),
 3.40 (d, $-\text{H}_{26}$),
 10 3.83 (s, $-\text{CH}_2-$ at 17),
 4.76 (s, $-\text{H}_{27}$),
 5.48 (d, $-\text{H}_{13}$),
 6.14 (d, $-\text{H}_{11}$),
 6.34 (mf, $>\text{NH}$ at 8),
 15 8.11 (s, $-\text{H}_{20}$)

N-Methyl-N-ethyl-2-aminoethanethiol can be obtained by a method similar to that described by D.D. Reynolds et al., J. Org. Chem. 26, 5125 (1961), from N-methyl-N-ethylamine (25 g) and ethylene thiocarbonate (43.7 g). After 20 distillation, N-methyl-N-ethyl-2-aminoethanethiol (1.3 g) is obtained in the form of a colourless liquid.

[B.p. (6.7 kPa) = 52°C.]

EXAMPLE 6

Using a method similar to that described in Example 1, but starting from 26-(3-dimethylaminopropyl)thio-
 25 pristinamycin II_B (50:50 A/B isomers) (9.8 g), trifluoroacetic acid (1.18 cc) and meta-chloroperbenzoic acid (3.1 g)

and after purification by "flash" chromatography [eluent: chloroform-methanol (80-20 by volume)], 15-cc fractions being collected, and concentrating fractions 53 to 75 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(3-dimethylaminopropyl)sulphonylpristinamycin II_B (mixed isomers) (1.6 g) is obtained in the form of a yellow powder melting at about 165°C.

NMR spectrum (mixture of isomers of type A₂ ≈ 45%, B₂ ≈ 35% and B₁ ≈ 15%):

10

1.53 (s, -CH₃ at 33 of B₂ and B₁),

1.75 (s, -CH₃ at 33 of A₂),

2.26, 2.28 and 2.32 (3s, >NCH₃ of the 3 isomers),

3.82 (s, >CH₂ at 17 of A₂),

3.70 and 3.88 (2d, >CH₂ at 17 of B₁),

15

3.69 and 3.91 (2d, >CH₂ at 17 of B₂),

4.76 (d, -H₂₇ of B₂),

5.25 (d, -H₂₇ of B₁),

5.50 (d, -H₁₃ of A₂),

7.63 (mt, >NH at 8 of B₂),

20

7.74 (mt, >NH at 8 of B₁),

7.82 (s, -H₂₀ of B₂ and B₁),

8.14 (s, -H₂₀ of A₂)

26-(3-Dimethylaminopropyl)thiopristinamycin II_B

can be obtained as follows:

25

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (5.25 g) and 3-dimethyl-aminopropanethiol (1.3 g), and after purification

by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 6 to 29 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(3-dimethylaminopropyl)thiopristinamycin II_B (3.3 g) is obtained in the form of a yellow powder melting at about 100°C.

NMR spectrum:

1.50 (s, 3H x 0.5 : -H₃₃ 1st isomer)
 1.70 (s, 3H x 0.5 : -H₃₃ 2nd isomer)
 1.80 (m, 2H : -SCH₂-CH₂-CH₂N<)
 2.20 (s, 6H x 0.5 : -N(CH₃)₂ 1st isomer)
 2.25 (s, 6H x 0.5 : -N(CH₃)₂ 2nd isomer)
 2.40 (m, 2H : -SCH₂-CH₂-CH₂N<)
 2.70 (m, 2H : -SCH₂-CH₂-CH₂N<)
 3.35 }
 3.45 } (2m, 1H : -H₂₆ of each isomer)
 4.60 }
 4.70 } (2d, 1H : -H₂₇ of each isomer)
 7.80 }
 8.10 } (2s, 1H : -H₂₀ of each isomer)

EXAMPLE 7

By using a method similar to that described in Example 1, but starting from 26-(2-diethylaminopropyl)-thiopristinamycin II_B (6.3 g), trifluoroacetic acid (0.72 cc) and meta-chloroperbenzoic acid (1.91 g), and

after purification by "flash" chromatography [eluent:
chloroform-methanol (90-10 by volume)], 60-cc fractions
being collected, and after concentrating fractions
7 to 9 to dryness under reduced pressure (2.7 kPa) at 30°C,
5 26-(2-diethylaminopropyl)sulphonylpristinamycin II_B
(isomers A₂) (0.99 g) is obtained in the form of a yellow
powder melting at about 150°C.

NMR spectrum:

10 1.03 to 1.20 (mt, -CH₂-CH(CH₃)N(CH₂CH₃)₂)
CH₃ at 32) (13)
1.76 (s, -CH₃ at 33)
3.82 (s, CH₂ at 17)
4.79 (m, -H₂₇)
5.53 (d, -H₁₃)
15 6.20 (d, -H₁₁)
6.42 (m, >NH at 8)
8.13 (s, -H₂₀)

After concentrating fractions 23 to 35 to dryness
under reduced pressure (2.7 kPa) at 30°C, 26-(2-diethyl-
20 aminopropyl)sulphonylpristinamycin II_B (isomers A₁)
(0.64 g) is obtained in the form of a beige-yellow powder
melting at about 160-170°C.

NMR spectrum:

25 1.14 (mt, -N(CH₂CH₃)₂)
1.24 (broad d, CH₃-CH-N<)
1.73 (s, -CH₃ at 33)
3.81 (borderline AB, >CH₂ at 17)

64

5.28 (d, -H₂₇)

5.43 (d, -H₁₃)

6.15 (d, -H₁₁)

6.88 (m, >NH at 8)

5 8.10 (s, -H₂₀)

P 26-(2-Diethylaminopropyl)thiopristinamycin II_B

can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (3.15 g) and 2-diethylaminopropanethiol (1.8 g), and after purification by "flash" chromatography [eluent: methylene chloride-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 3 to 5 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-diethylaminopropyl)thiopristinamycin II_B (1.4 g) is obtained in the form of a yellow powder melting at about 160°C.

NMR spectrum:

20
TO680X
P
1 (m, 9H : -H₃₂ + -N(CH₂CH₃)₂),
2.50 (m, 6H : -S-CH₂-CH-N(CH₂CH₃)₂),
3.30 (m, 1H : -H₂₆),
4.70 (d, 1H : -H₂₇),
8.12 (s, 1H : -H₂₀)

2-diethylaminopropanethiol can be prepared as follows:

25 *P* A 10 N aqueous solution of sodium hydroxide (25 cc) is added to a solution of 3-S-isothioureido-2-diethylaminopropane dihydrochloride (29.5 g) in distilled water (150 cc).

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The mixture is heated to 100°C for 1 hour, cooled to 20°C, adjusted to pH 9 by adding a 12 N aqueous solution of hydrochloric acid (8 cc), and is then extracted with ethyl ether (3 x 100 cc). The ether phases are combined, dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The mixture is purified by distillation.

2-Diethylamino-1-propanethiol (5.8 g) is obtained in the form of a colourless liquid. [B.p. (2.7 kPa) = 78°C.]

10 *P* 1-S-Isothioureido-2-diethylaminopropane dihydrochloride can be prepared as follows:

P Thiourea (16.7 g) is added to a solution of 1-chloro-2-diethylaminopropane hydrochloride (41 g) in dimethylformamide (200 cc). The mixture is heated to 15 100°C for 30 minutes, and then cooled to 20°C. The white precipitate formed is collected by filtration, washed with dimethylformamide (3 x 20 cc) and then with ethyl ether (3 x 20 cc). 1-S-Isothioureido-2-diethylaminopropane dihydrochloride (29.6 g) is obtained in the form 20 of white crystals melting at 247-249°C.

P 1-Chloro-2-diethylaminopropane hydrochloride can be obtained as follows:

P 2-Diethylaminopropanol hydrochloride (45.2 g) is added over 15 minutes to thionyl chloride (100 cc) and 25 the mixture is heated to 80°C. After 2 hours' stirring, excess thionyl chloride is distilled off and the residue is taken up with ethyl ether (200 cc). 1-Chloro-2-diethyl-

69

aminopropane hydrochloride crystallizes out. After filtration, white crystals (48.2 g) melting at 112°C are obtained.

5 *P* 2-Diethylaminopropanol hydrochloride can be obtained as follows:

P A solution of ethyl 2-diethylaminopropionate (66 g) in ethyl ether (330 cc) is added slowly at 20°C to a suspension of lithium aluminium hydride (10.6 g) in ethyl ether (1 litre) kept under nitrogen. The reaction is maintained for 5 hours at a temperature of 35°C , and the temperature is then lowered to 0°C . Water (12.4 cc), a 5 N aqueous solution of sodium hydroxide (9.1 cc) and then water (41.3 cc) are then added dropwise at 0°C , the mixture is stirred for 30 minutes and is then filtered
15 through sintered glass and is then washed with ethyl ether. The ether phase is dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C . A yellow liquid (43.8 g) is obtained and is dissolved in acetone (200 cc), to which a
20 4.5 N solution (78 cc) of hydrogen chloride gas in ethyl ether is then added. 2-Diethylaminopropanol hydrochloride crystallizes out. After filtration, white crystals (45.2 g) melting at $97-100^{\circ}\text{C}$ are obtained.

P Ethyl 2-diethylaminopropionate can be obtained
25 according to Braun et al., Beilstein, 61, 1425 (1928).

U EXAMPLE 8

P The method used is similar to that described in

Example 2, but starting from 26-(2-diethylaminopropyl)-
thiopristinamycin II_B (isomers A) (4 g), 98 % meta-
chloroperbenzoic acid (1.16 g) and solid sodium bicarbo-
nate (1 g). After purification by "flash" chromatography
5 [eluent: chloroform-methanol (93-7 by volume)] and concen-
trating fractions 21 to 48 to dryness under reduced
pressure (2.7 kPa) at 30°C, 25-cc fractions being col-
lected, 26-(2-diethylaminopropyl)sulphinylpristinamycin
II_B (isomers A₂) (2.69 g) is obtained in the form of a
10 yellow powder which has characteristics identical to
those of the product obtained in Example 7.

26-(2-Diethylaminopropyl)thiopristinamycin II_B
(isomer A) can be obtained by using a method similar to
that described in Example 1, but starting from pristina-
15 mycin II_A (15 g) and 2-diethylaminopropanethiol (4.62 g).
After purification by "flash" chromatography [eluent:
chloroform-methanol (90-10 by volume)] and concentrating
fractions 27 to 52 to dryness under reduced pressure
(2.7 kPa) at 30°C, 40-cc fractions being collected, a
20 yellow solid (12 g) is obtained and stirred in ethyl ether
(60 cc), filtered off and then dried. 26-(2-Diethylamino-
propyl)thiopristinamycin II_B (isomer A) (8.2 g) is ob-
tained in the form of a light-yellow powder melting at
about 122°C.

25

NMR spectrum:

1 to 1.15 (mt, ethyl-CH₃ + CH₃-CH-N(C₂H₅)₂)
1.70 (s, -CH₃ at 33)

2.35 to 2.60 (mt, $-N \begin{cases} \text{CH}_2-\text{CH}_3 \\ \text{CH}_2-\text{CH}_3 \end{cases}$)

2.50 to 3.10 (mt, $-\text{SCH}_2\text{CH}-$)

2.75 (mt, $-\text{H}_4$)

5 2.89 and 3.05 (2dd) } $>\text{CH}_2$ at 15)
2.92 and 3.08 (2dd)

3.30 (mt) } $-\text{H}_{26}$
10 3.37 (mt)

3.80 (s, $>\text{CH}_2$ at 17)

4.69 (d) } $-\text{H}_{27}$
4.71 (d)

15 5.45 (d, $-\text{H}_{13}$)

6.13 (d) } $-\text{H}_{11}$
6.14 (d)

6.4 to 6.60 (mt, $>\text{NH}$ at 8)

20 6.51 (dd) } $-\text{H}_5$
6.53 (dd)

8.09 (s, $-\text{H}_{20}$)

25 2-Diethylaminopropanethiol can be obtained as described earlier in Example 7.

EXAMPLE 9

The method used is similar to that described in

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Example 2 but starting from 26-(1-diethylamino-2-propyl)-
thiopristinamycin II_B (isomers A) (4.58 g), 98% meta-
chloroperbenzoic acid (1.29 g) and solid sodium bicarbo-
nate (1.14 g). After purification by "flash" chromato-
5 graphy [eluent: chloroform-methanol (97-3 by volume)],
20-cc fractions being collected, and concentrating, res-
pectively, fractions 59 to 77 and fractions 79 to 97 under
reduced pressure (2.7 kPa) at 30°C, there are obtained:
from fractions 79 to 97, 26-(1-diethylamino-2-propyl)-
10 sulphinylpristinamycin II_B (first isomer) (1.47 g) in
the form of a light-yellow solid melting at about 132°C

NMR spectrum:

1.02 (t, ethyl-CH₃)

1.34 (d, CH₃-CH-CH₂N(C₂H₅)₂)

15 1.72 (s, -CH₃ at 33)

2.5 to 2.7 (mt, -CH₂-N $\begin{matrix} \text{CH}_2^- \\ \text{CH}_2^- \end{matrix}$)

2.77 (mt, -H₄)

2.87 and 3.09 (2dd, >CH₂ at 15)

20 2.97 (mt, -S-CH<)
↓
O

3.72 (mt, -H₂₆)

3.80 (s, >CH at 17)

4.92 (mt, -H₂₇)

25 5.43 (d, -H₁₃)

6.15 (d, -H₁₁)

6.72 (dd, >NH at 8)

13

8.06 (s, -H₂O)

and from fractions 59 to 77, 26-(1-diethylamino-2-propyl)-sulphonylpristinamycin II_B (second isomer) (1.07 g) in the form of a light-yellow solid melting at about 128°C.

NMR spectrum:

1.72 (s, CH₃ at 33)

3.4 (mt, -H₂6)

3.79 (s, CH₂ at 17)

4.74 (mt, -H₂7)

5.48 (d, -H₁3)

6.18 (d, -H₁1)

6.80 (mf, >NH at 8)

8.09 (s, -H₂O)

26-(1-Diethylamino-2-propyl)thiopristinamycin II_B

(isomers A) can be obtained by using a method similar to that described in Example 1 but starting from pristina-mycin II_A (13 g) and 1-diethylamino-2-propanethiol (4 g). After purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 46 to 55 to dryness under reduced pressure (2.7 kPa) at 30°C, 50-cc fractions being collected, a pale yellow solid (8 g) is obtained and recrystallized from acetonitrile (30 cc). After filtration and drying, 26-(2-diethylamino-2-propyl)thiopristinamycin II_B (iso-mers A) (5.91 g) is obtained in the form of white crystals melting at 136°C.

P

NMR spectrum:

0.9 to 1.10 (mt, $-N(CH_2CH_3)_2$)

1.33 to 1.37 (2d, $CH_3-\underset{|}{CH}-CH_2N<$)

1.7 (s, $-CH_3$ at 33)

5

2.4 to 2.65 (mt, $-CH_2N \begin{matrix} \swarrow CH_2- \\ \searrow CH_2- \end{matrix}$)

2.76 (mt, $-H_4$)

3 (mt, $-S-CH<$)

2.9 and 3.1 (2dd, $>CH_2$ at 15)

10

3.52 (mt, $-H_{26}$)

3.81 (s, $>CH_2$ at 17)

4.78 (mt, $-H_{27}$)

5.46 (d, $-H_{13}$)

6.14 (d, $-H_{11}$)

15

6.40 (mt, $>NH$ at 8)

8.09 and 8.10 (2s, $-H_{20}$)

P

1-Diethylamino-2-propanethiol can be obtained according to the method described by R.T. Wragg, J. Chem. Soc. (C), 2087 (1969).

20 EXAMPLE 10

P

A method similar to that described in Example 2 is used, but starting from 26-[(2R)-2-dimethylaminobutyl]-thiopristinamycin IIg (isomer A) (1.7 g), sodium bicarbonate (0.50 g) and 98% meta-chloroperbenzoic acid (0.45 g).

25 After purification by "flash" chromatography [eluent: ethyl acetate-methanol (85-15 by volume)] and concentrating fractions 35 to 58 to dryness under reduced pressure

(15)

(2.7 kPa) at 30°C, a white solid (1.1 g) is obtained which is stirred in ethyl ether (30 cc). After filtration and drying, 26-[(2R)-2-dimethylaminobutyl]sulphinylpristinamycin IIg (isomer A₂) (0.95 g) is obtained in the form of a white solid melting at about 126°C.

NMR spectrum:

1 (mt, >N-CH-CH₂CH₃)

1.45 to 1.75 (mt, >N-CH-CH₂CH₃)

1.78 (s, -CH₃ at 33)

2.50 to 3.05 (mt, -S-CH₂-CH< and -H₄)

2.93 and 3.14 (2dd, >CH₂ at 15)

3.31 (mt, -H₂₆)

3.84 (s, >CH₂ at 17)

4.84 (d, -H₂₇)

5.51 (d, -H₁₃)

6.19 (d, -H₁₁)

6.30 (dd, >NH at 8)

8.15 (s, -H₂₀)

26-[(2R)-2-Dimethylaminobutyl]thiopristinamycin IIg (isomer A) can be obtained by using a method similar to that described in Example 1 but starting from pristinamycin II_A (8 g) and (2R)-2-dimethylaminobutanethiol.

After purification by "flash" chromatography [eluent:

dichloromethane-methanol (90-10 by volume)] and concentrating fractions 36 to 55 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-[(2R)-2-dimethylaminobutyl]-

thiopristinamycin II_B (isomer A) (3 g) is obtained in the form of a light-yellow solid melting at about 120°C.

Crystallization of this product (0.9 g) from acetonitrile (5 cc) produces, after separation by filtration,

5 26-[(2R)-2-dimethylaminobutyl]thiopristinamycin II_B (isomer A) (0.2 g) in the form of white crystals melting at 122°C.

NMR spectrum:

1 (mt, $\text{>N-CH-CH}_2\text{CH}_3$)

10 1.4 to 1.7 (mt, $\text{>N-CH-CH}_2\text{CH}_3$)

1.72 (s, -CH_3 at 33)

2.30 (s, $\text{-N(CH}_3)_2$)

2.5 to 2.85 (mt, $\text{-S-CH}_2\text{-CH<}$ and -H_4)

2.93 and 3.10 (2dd, >CH_2 at 15)

15 3.34 (broad d, -H_{26})

3.83 (s, >CH_2 at 17)

4.76 (broad s, -H_{27})

5.48 (d, -H_{13})

6.14 (d, -H_{11})

20 6.26 (dd, >NH at 8)

8.13 (s, -H_{20})

(R)-2-Dimethylaminobutanethiol can be obtained using a method similar to that described below in Example 11, starting from triphenylphosphine (52.4 g), diisopropyl azodicarboxylate (40 cc), (R)-2-dimethylaminobutanol (12 g) and thiolacetic acid (15.2 cc) (in this case, the intermediate thioester is hydrolysed directly during the

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chromatography on silica gel).

After purification by "flash" chromatography
[eluent: dichloromethane : 1000 cc, then dichloromethane-
methanol (85-15 by volume) : 2000 cc, then dichloromethane-
5 methanol (80-20 by volume) : 4000 cc], 100-cc fractions
being collected, and concentrating fractions 42 to 60 to
dryness under reduced pressure, a yellow oil (14 g) is
obtained, which is purified by distillation. In this
manner, (R)-2-dimethylaminobutanethiol (2.4 g) is obtained
10 in the form of a colourless liquid. [B.p. (4 kPa) = 70-
75°C].

(R)-2-Dimethylamino-1-butanol can be obtained by
a method identical to that described by M. Wenghoefer et
al., J. Heterocycl. Chem., 7(6), 1407 (1970).

EXAMPLE 11

26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopris-
tinamycin II_B (isomer A) (2.67 g), sodium bicarbonate
(0.7 g) and 98% meta-chloroperbenzoic acid (0.7 g), after
purification by "flash" chromatography [eluent: chloro-
20 form-methanol (90-10 by volume)], 20-cc fractions being
collected, and concentrating fractions 19 to 23 to dryness
under reduced pressure (2.7 kPa) at 30°C, a light-yellow
solid (1.3 g) is obtained, which is stirred in ethyl ether
(50 cc), and separated off by filtration to give 26-[(2S)-
25 2-dimethylamino-3-phenylpropyl]sulphonylpristinamycin II_B
(isomer A₂) (1.18 g) in the form of a light-yellow solid
melting at about 150°C.

NMR spectrum (400 MHz, CDCl₃)

1.73 (s, -CH₃ at 33)

2.4 to 2.6 (mt, $\left. \begin{array}{c} \text{-S-CH}_2\text{-C} \begin{array}{l} \text{H} \\ \text{CH}_2\text{-} \end{array} \end{array} \right\}$)

2.8 to 3.15 (mt,)

2.44 (s, -N(CH₃)₂)

2.77 (mt, -H₄)

2.89 and 3.1 (2dd, >CH₂ at 15)

3.18 (mt, -H₂₆)

3.82 (s, >CH₂ at 17)

4.68 (d, -H₂₇)

5.51 (d, -H₁₃)

6.19 (d, -H₁₁)

6.50 (dd, >NH at 8)

7.18 (d, phenyl ortho-H)

7.23 (t, phenyl para-H)

7.31 (t, phenyl meta-H)

8.13 (s, -H₂₀)

An aqueous solution containing 1% of 26-[(2S)-2-

dimethylamino-3-phenylpropyl]sulphonylpristinamycin II_B

(isomer A₂) is obtained with:

product 30 mg

0.1 N hydrochloric acid 0.45 cc

distilled water q.s. 3 cc

26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopris-

tinamycin II_B (isomer A) can be prepared by using a

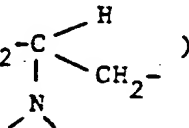
method similar to that described in Example 1 for the

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preparation of the starting material, but starting from
 pristinamycin II_A (7.13 g) and (S)-2-dimethylamino-3-
 phenylpropanethiol (2.65 g) and after purification by
 "flash" chromatography [eluent: ethyl acetate-methanol
 5 (80-20) by volume)], 60-cc fractions being collected, and
 concentrating fractions 33 to 43 to dryness under reduced
 pressure (2.7 kPa) at 30°C, a light-yellow solid (4.6 g)
 is obtained which is stirred in ethyl ether (50 cc), fil-
 tered off and then dried under reduced pressure (90 Pa)
 10 at 45°C. In this manner, 26-[(2S)-2-dimethylamino-3-
 phenylpropane]thiopristinamycin II_B (isomer A) (3.6 g)
 is obtained in the form of a pale yellow powder melting
 at about 110°C.

NMR spectrum:

- 15 1.69 (s, -CH₃ at 33)
 2.38 (s, -N(CH₃)₂)
 2.35 to 3.05 (mt, -SCH₂-C^H₂-N₂)
 2.73 (mt, -H₄)
 2.89 and 3.10 (2dd, >CH₂ at 15)
 3.26 (broad d, -H₂₆)
 3.81 (s, >CH₂ at 17)
 4.68 (broad s, -H₂₇)
 25 5.47 (d, -H₁₃)
 6.12 (d, -H₁₁)



6.27 (mf, > NH at 8)
7.18 (d, phenyl ortho-H)
7.21 (t, phenyl para-H)
7.30 (t, phenyl meta-H)

5

8.11 (s, -H₂O)

(S)-2-Dimethylamino-3-phenylpropanethiol can be prepared as follows:

P Sodium methoxide (0.2 g) is added under a nitrogen atmosphere to (S)-2-dimethylamino-3-phenylpropanethiol-
10 acetate (20 g: crude) dissolved in methanol (50 cc) and the mixture is heated under reflux for 2 hours. The mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give a liquid which is purified by distillation. (S)-2-Dimethylamino-3-phenylpropanethiol
15 (2.4 g) is obtained in the form of a colourless liquid [b.p. (14 Pa) = 95°C] which is used as such in the reaction which follows.

P (S)-2-Dimethylamino-3-phenylpropanethiolacetate can be prepared as follows:

20 *P* Triphenylphosphine (41.97 g) and tetrahydrofuran (310 cc) are added at 0°C under a nitrogen atmosphere, and then diisopropyl azodicarboxylate (31.5 cc) is added dropwise and the mixture is left stirred for half an hour at 0°C. A mixture of (S)-2-dimethylamino-3-phenylpro-
25 panol (15 g) and of thiolacetic acid (11.44 cc) dissolved in tetrahydrofuran (160 cc) is added dropwise to the white suspension obtained. After being stirred for 1 hour at

0°C and then for 1 hour 30 minutes at 25°C, the mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. Methanol (190 cc) is added to the oil obtained, the white solid which precipitates is removed by filtration, and the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is then stirred with isopropyl ether (200 cc), the white solid precipitated is again removed by filtration and the filtrate is concentrated to give a yellow oil (45 g), which is purified by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)], 100-cc fractions being collected. After concentrating fractions 37 to 55 to dryness under reduced pressure (2.7 kPa) at 30°C, (S)-2-dimethylamino-3-phenylpropanethiolacetate (10.4 g) is obtained in the form of an orange-yellow oil (containing triphenylphosphine oxide).

(S)-2-Dimethylamino-3-phenylpropanol can be prepared by using a method similar to that described by T. Hayashi et al., J. Org. Chem., 48, 2195 (1983).

20 EXAMPLE 12

By using a method similar to that described in Example 1, but starting from 26-[2-(1-pyrrolidinyl)ethyl]-thiopristinamycin II_B (90% isomer A), trifluoroacetic acid (1.47 cc), and meta-chloroperbenzoic acid (3.86 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 30-cc fractions being collected, and concentrating fractions 18 to 25

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to dryness under reduced pressure (2.7 kPa) at 30°C, 26-[2-(1-pyrrolidinyl)ethyl]sulphinypristinamycin II_B (isomers: 60% A₁, 25% A₂, 15% B₁) (3.9 g) is obtained in the form of a yellow powder melting at about 175°C.

NMR spectrum (isomer A₁):

1.74 (s, -CH₃ at 33)

2.62 (mt, -N $\begin{matrix} \text{CH}_2^- \\ \text{CH}_2^- \end{matrix}$)

2.70 to 3.20 (mt, >CH₂ at 15, -S-CH₂CH₂N $\begin{matrix} \text{CH}_2^- \\ \text{CH}_2^- \end{matrix}$, -H₄)

3.81 (s, >CH₂ at 17)

5.28 (broad s, -H₂₇)

5.45 (d, -H₁₃)

6.14 (d, -H₁₁)

6.58 (mt, >NH at 8)

8.12 (s, -H₂₀)

After concentrating fractions 26 to 43 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-[2-(1-pyrrolidinyl)ethyl]sulphinypristinamycin II_B (75% isomer A₂, 5% isomer A₁, 10% isomer B₁, 10% isomer B₂) (4.36 g) is obtained in the form of a yellow powder melting at about 145°C.

NMR spectrum (isomer A₂):

1.76 (s, -CH₃ at 33)

1.82 (m, >CH₂ at 3- and 4- of pyrrolidinyl)

2.63 (mt, $-N-CH_2-$)
 $\quad \quad \quad |$
 $\quad \quad \quad CH_2-$

2.85 to 3.20 (mt, $-S-CH_2-CH_2-$ and $>CH_2$ at 15)

3.82 (s, $>CH_2$ at 17)

5 4.84 (dd, $-H_3 + d, -H_{27}$)

5.51 (d, $-H_{13}$)

6.18 (d, $-H_{11}$)

6.47 (mt, $>NH$ at 8)

8.13 (s, $-H_{20}$)

10 26-[2-(1-Pyrrolidinyl)ethyl]thiopristinamycin IIg

can be prepared as follows:

By using a method similar to that described in Example 3 but starting from pristinamycin IIa (5.25 g) and 2-(1-pyrrolidinyl)ethanethiol (1.7 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)] of 2-(1-pyrrolidinyl)ethanethiol, and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)] and concentrating fractions 19 to 60 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-[2-(1-pyrrolidinyl)ethyl]thiopristinamycin IIg (3.9 g) is obtained in the form of a yellow powder melting at about 115°C.

NMR spectrum:

1.90 (mt, 4H : $-N-\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}$)

2.50 to 2.80 (m, 6H : $-S-CH_2-CH_2-N\begin{array}{c} H_2C \\ | \\ CH_2 \end{array}$)

25

3.40 (d, 1H : -H₂₆)

4.75 (d, 1H : -H₂₇)

8.10 (s, 1H, -H₂₀)


f 2-(1-Pyrrolidinyl)ethanethiol can be prepared
5 according to the method described by J.W. Haeffele and
R.W. Broge, Proc. Sci. Toilet Goods Assoc. 32, 52 (1959)
[Chem. Abstr. 54, 17234e (1960)].

u EXAMPLE 13

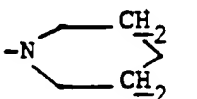
f By using a method similar to that described in
10 Example 1, but starting from 26-(2-piperidinoethyl)thio-
pristinamycin II_B (isomer A) (6 g), trifluoroacetic acid
(0.69 cc) and 85% meta-chloroperbenzoic acid (1.82 g),
after purification by "flash" chromatography [eluent:
chloroform-methanol (85-15 by volume)], 20-cc fractions
15 being collected and concentrating fractions 52 to 105
to dryness under reduced pressure (2.7 kPa) at 30°C, a
yellow solid (4.7 g) is obtained, which is again purified
by "flash" chromatography [eluent: chloroform-methanol
(85-15 by volume)], 5-cc fractions being collected.
20 After concentrating fractions 92 to 99 under reduced pres-
sure (2.7 kPa) at 30°C, a yellow solid (1.83 g) is obtai-
ned, which is stirred in ethyl ether (20 cc), separated
off by filtration, and then dried under reduced pressure
(90 Pa) at 30°C. In this manner, 26-(2-piperidinoethyl)-
25 thiopristinamycin II_B (isomers: 90% A₂, 10% A₁) (1.51 g)
is obtained in the form of a yellow powder melting at
about 162°C.

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P NMR spectrum (400 MHz, CDCl₃)

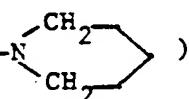
1.52 (mf, )

5


1.70 (mf, )

1.78 (s, -CH₃ at 33)

10

2.64 (mf, )

2.80 (mt, -H₄)

2.85 to 3.25 (mt, -S-CH₂-CH₂-N<)


2.94 and 3.15 (2dd, >CH₂ at 15)

15

3.20 (mt, -H₂₆)

3.83 (s, >CH₂ at 17)

4.92 (d, -H₂₇)

5.54 (d, -H₁₃)

6.24 (d, -H₁₁)

20

6.70 (mf, >NH at 8)

8.14 (s, -H₂₀)

P After concentrating fractions 100 to 140 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (2.11 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30°C. 26-(2-Piperidinoethyl)-thiopristinamycin II_B (isomers: 50% A₁, 50% A₂) (1.75 g)

is obtained in the form of a yellow powder melting at about 152°C.

5 ³⁰P NMR spectrum (400 MHz, CDCl₃)
1.74 (s, ^β-CH₃ at 33 isomer A₁)
1.78 (s, ^β-CH₃ at 33 isomer A₂)
3.20 (mt, -H₂₆ isomer A₂)
3.46 (mt, -H₂₆ isomer A₁)
3.82 (borderline AB, ^δCH₂ at 17 isomer A₁)
3.83 (s, ^δCH₂ at 17 isomer A₂)
10 4.90 (d, ^β-H₂₇ isomer A₂)
5.30 (s, -H₂₇ isomer A₁)
5.52 (d, -H₁₃ isomer A₁)
5.54 (d, -H₁₃ isomer A₂)
6.60 (dd, -H₅ isomer A₂)
15 6.70 (dd, -H₅ isomer A₁)
8.14 (s, -H₂₀, isomers A₂ and A₁)

26-(2-Piperidinoethyl)thiopristinamycin II_B
(isomer A) can be obtained as follows:


20 ³⁰P By using a method similar to that described in
Example 1, but starting from pristinamycin II_A (11.8 g)
and 2-piperidinoethanethiol (3.58 g), and after purification by "flash" chromatography [eluent: chloroform-
methanol (85-15 by volume)], 60-cc fractions being collected, and concentrating fractions 24 to 31 to dryness under
25 reduced pressure (2.7 kPa) at 30°C, 26-(2-piperidino-
ethyl)thiopristinamycin II_B (isomer A) (8.3 g) is obtained in the form of a light-yellow powder melting at

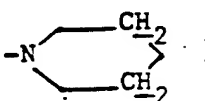
87

about 120^oc.

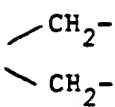
P NMR spectrum:

1.08 (d, -CH₃ at 32)

5 1.40 to 1.60 (mt, -N  CH₂)

1.60 to 1.80 (mt, -N )

1.73 (s, -CH₃ at 33)

10 2.45 to 2.90 (mt, -S-CH₂-CH₂-N-N )

3.43 (mt, -H₂₆)

3.82 (s, >CH₂ at 17)

4.71 (broad s, -H₂₇)

5.50 (d, -H₁₃)

15 8.13 (s, -H₂₀)

P 2-Piperidinoethanethiol can be obtained by a method identical to that described by D.D. Reynolds, D.L. Fields and D.J. Johnson, J. Org. Chem., 26, 5125 (1961).

CL EXAMPLE 14

20 *P* By using a method similar to that described in Example 2, but starting from 26-[2-(1-imidazolyl)ethyl]-thiopristinamycin II_B (isomers: 85% A, 15% B) (3.2 g), sodium bicarbonate (1 g) and 98% meta-chloroperbenzoic acid (0.93 g), after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 25-cc fractions being collected, and concentrating fractions 29 to 49 to dryness under reduced pressure (2.7 kPa)

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at 30°C, a yellow solid (1.4 g) is obtained. The solid obtained is purified again by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 10-cc fractions being collected. After concentrating fractions 47 to 55 to dryness under reduced pressure (2.7 kPa) at 30°C, a light-yellow solid (0.62 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40°C. In this manner, 26-[2-(1-imidazolyl)ethyl]sulphonyl-pristinamycin II_B (isomer A₂) (0.6 g) is obtained in the form of a yellow solid melting at about 170°C.

1 NMR spectrum (400 MHz, CDCl_3)

1.80 (s, $-\text{CH}_3$ at 33)

2.72 (mt, -H₄)

15 2.97 to 3.09 (2dd, γCH_2 at 15)

3.0 (mt, -H₂6 and one H of -S-CH₂-)

3.48 (mt, the other H of -S-CH₂-)

3.82 (borderline AB, >CH_2 at 17)

4.53 (dd, γ N-CH₂-)

4.77 (d, -H₂₇)

5.52 (d, -H₁₃)

6.16 (d, $-H_{11}$)

2.5 6.46 (dd, \geq NH at 8)

7.12 (s, $-N-CH=CH-N=$)

7.69 (s, $\geq N-CH=N-$)

8.16 (s, -H₂O)

P 26-[2-(1-imidazolyl)ethyl]thiopristinamycin II_B
can be prepared by using a method similar to that described
in Example 3, but starting from pristinamycin II_A (14.35 g)
5 and 2-(1-imidazolyl)ethanethiol (3.5 g), after stirring
at 20°C for 18 hours followed by purification by "flash"
chromatography [eluent: ethyl acetate-methanol (80-20 by
volume)] and concentrating fractions 34 to 59 to dryness
under reduced pressure (2.7 kPa) at 30°C; a yellow solid
10 is obtained, which is stirred in ethyl ether (60 cc) and
then separated off by filtration, to give 26-[2-(1-imidazo-
lyl)ethyl]thiopristinamycin II_B (isomers: 85% A, 15%
B) (10.9 g) in the form of a yellow solid melting at
about 160°C.

15

P NMR spectrum:

1.53 (s, -CH₃ at 33 of B),

1.73 (s, -CH₃ at 33 of A),

2.74 (mt, -H₄ of A),

2.86 and 3.14 (2dd, >CH₂ at 15 of A),

20

2.85 to 3.05 (mt, -SCH₂-),

3.11 (mt, -H₂₆ of A),

3.32 (mt, -H₂₆ of B),

3.82 (borderline AB, >CH₂ at 17 of A),

4.15 to 4.30 (mt, -CH₂N<),

25

4.58 (d, -H₂₇ of B),

4.68 (fine d, -H₂₇ of A),

5.44 (d, -H₁₃ of A),

6.16 (d, ¹³H₁₁ of A),
6.83 (dd, >NH at 8 of A),
6.97 and 7.08 (2s, >N-CH=CHN< of B),
7.01 and 7.10 (2s, >N-CH=CHN< of A),
5 7.54 (s, >N-CH=N- of B),
7.61 (s, >N-CH=N- of A),
7.64 (mt, >NH at 8 of B),
7.82 (s, -H₂O of B),
8.09 (s, -H₂O of A)

10 2-(1-Imidazolyl)ethanethiol can be prepared by a
method similar to that described in Example 11 for the
preparation of the starting material, but starting from
2-(1-imidazolyl)ethanethiolacetate (21 g) and sodium
methoxide (0.5 g). After purification by distillation,
15 2-(1-imidazolyl)ethanethiol (2.3 g) is obtained in the
form of an oil [b.p. (20 Pa) = 99.5°C].

2-(1-Imidazolyl)ethanethiolacetate can be prepared
by a method similar to that described in Example 11 for
the preparation of the starting material, but starting from
20 2-(1-imidazolyl)ethanol (15 g), triphenylphosphine (70.2 g),
diisopropyl azodicarboxylate (55.8 cc) and thiolacetic acid
(21 cc). After purification by "flash" chromatography
[eluent: methylene chloride (1500 c), followed by ethyl
acetate-methanol (80-20 by volume)], 100-cc fractions be-
25 ing collected, and concentrating fractions 21 to 35 to
dryness under reduced pressure (2.7 kPa) at 30°C, 2-(1-
imidazolyl)ethylthiolacetate (21.14 g) is obtained in the

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form of an orange-yellow oil which is used without further purification.

2-(1-Imidazolyl)ethanol can be prepared by a method similar to that described by J. Geibel et al., J. Am. Chem. Soc., 100, 3575 (1978).

EXAMPLE 15

By using a method similar to that described in Example 2, but starting from 26-(2-morpholinoethyl)thiopristinamycin II_B (isomer A) (5.5 g), sodium bicarbonate (1.3 g), and 98% meta-chloroperbenzoic acid (1.4 g), after extraction of the reaction mixture, drying of the organic phase over magnesium sulphate, filtering and concentrating to dryness under reduced pressure (2.7 kPa) at 30°C, a light-yellow solid is obtained, which is stirred in isopropyl ether (100 cc), separated off by filtration, and then dried under reduced pressure (90 Pa) at 35°C. In this manner, 26-(2-morpholinoethyl)sulphinylpristinamycin II_B (isomer A₂) (4.8 g) is obtained in the form of a light-yellow solid melting at about 126°C.

NMR spectrum:

1.77 (s, -CH₃ at 33)

2.6 to 3.1 (mt, $\begin{array}{c} \text{-SCH}_2\text{-CH}_2\text{N} \begin{array}{l} \text{CH}_2\text{-} \\ \text{CH}_2\text{-} \end{array} \\ \downarrow \\ \text{O} \end{array}$ and -H₄)

2.95 and 3.13 (2dd, >CH₂ at 15)

3.20 (mt, -H₂₆)

3.78 (mt, -CH₂-O-CH₂-)

3.81 (s, >CH_2 at 17)

4.85 (mt, $-\text{H}_{27}$)

5.53 (d, $-\text{H}_{13}$)

6.20 (d, $-\text{H}_{11}$)

5 6.53 (mf, >NH at 8)

8.14 (s, $-\text{H}_{20}$)

P

26-(2-Morpholinoethyl)thiopristinamycin II_B

(isomer A) can be obtained by a method similar to that described in Example 1, but starting from pristinamycin
10 II_A (15 g) and 2-morpholinoethanethiol (6.3 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (75-25 by volume)], 30-cc fractions being collected, and concentrating fractions 35 to 49 to dryness under reduced pressure (2.7 kPa) at 30°C , a beige
15 solid (11 g) is obtained which is crystallized from acetonitrile (120 cc). In this manner, 26-(2-morpholinoethyl)-thiopristinamycin II_B (isomer A) (5.7 g) is obtained in the form of white crystals melting at 132°C .

P

NMR spectrum:

20 1.73 (s, $-\text{CH}_3$ at 33)

2.50 (mf, $-\text{N} \begin{array}{l} \text{CH}_2^- \\ \text{CH}_2^- \end{array}$)

2.6 to 2.9 (mt, $-\text{H}_4$)

2.64 (mt, >N-CH_2-)

2.79 (mt, $-\text{SCH}_2-$)

2.91 and 3.11 (2dd, >CH_2 at 15)

15

1/0930

25

3.37 (broad d, -H₂₆)

3.74 (mf, $\text{O} \begin{array}{l} \diagup \text{CH}_2^- \\ \diagdown \text{CH}_2^- \end{array}$)

5 3.83 (s, >CH₂ at 17)

4.74 (broad s, -H₂₇)

5.45 (d, -H₁₃)

6.13 (d, -H₁₁)

6.28 (mf, >NH at 8)

10 8.13 (s, -H₂₀)

P 2-Morpholinoethanethiol can be prepared by a method similar to that described by D.D. Reynolds et al., J. Org. Chem., 26, 5125 (1961).

U EXAMPLE 16

15 *P* By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) (5.8 g), trifluoroacetic acid (0.68 cc) and meta-chloroperbenzoic acid (1.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)],
20 15-cc fractions being collected, and concentrating fractions 9 to 15 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-butylaminoethyl)sulphinypristinamycin II_B (70% isomer A₂, 15% isomer B₁, 15% isomer B₂) (1.7 g)
25 is obtained in the form of a yellow powder melting at about 140°C.

20

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P NMR spectrum (isomer A₂):

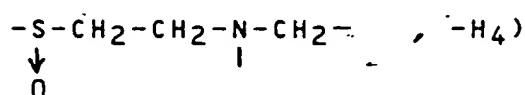
0.85 to 1.00 (mt, -CH₃ at 31 and 30 + chain -CH₃)

1.34 (mt, -CH₂CH₃)

1.48 (mt, -CH₂CH₂CH₂CH₃)

5 1.75 (s, -CH₃ at 33)

2.50 to 3.30 (mt, -H₂₆, >CH₂ at 2,



3.80 (s, >CH₂ at 17)

4.80 (d, -H₂₇)

5.50 (d, -H₁₃)

6.17 (d, -H₁₁)

6.40 (dd, >NH at 8)

8.12 (s, -H₂₀)

15 *P* After concentrating fractions 18 to 24 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-butyl-aminoethyl)sulphinypristinamycin II_B (85% isomer A₁, 15% isomer B₁) (0.5 g) is obtained in the form of a yellow powder melting at about 170°C.

20 *P* NMR spectrum (isomer A₁):

0.85 to 1.00 (mt, -CH₃ at 31, 30 and chain -CH₃)

1.33 (mt, -CH₂CH₃)

1.47 (mt, -CH₂CH₂CH₂CH₃)

1.71 (s, -CH₃ at 33)

2.50 to 3.25 (mt, -S-CH₂CH₂N< and -H₄)



3.79 (borderline AB, >CH₂ at 17)

5.26 (d, -H₂₇)

5.44 (d, -H₁₃)

6.13 (d, -H₁₁)

6.62 (mt, >NH at 8)

5 8.10 (s, -H₂₀)

P 26-(2-Butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) can be prepared as described below in Example 17.

EXAMPLE 17

10 P By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin II_B (isomer B) (3.15 g), trifluoroacetic acid (0.37 cc) and meta-chloroperbenzoic acid (0.97 g), and after purification by "flash" chromatography [eluent:
15 chloroform-methanol (90-10 by volume)], 15-cc fractions being collected, and concentrating fractions 18 to 35 to dryness under reduced pressure (2.7 kPa) at 30°C, 26E (2-butylaminoethyl)sulphinypristinamycin II_B (65% isomer B₁, 35% isomer B₂) (1.18 g) is obtained in the
20 form of a yellow powder melting at about 140°C.

P NMR spectrum:

0.90 to 1.05 (mt, -CH₃ at 30 and 31 and chain
-CH₃ of B₁ and B₂)

1.40 (mt, -CH₂CH₃ of B₁ and B₂)

1.50 (mt, -CH₂CH₂CH₂CH₃ of B₁ and B₂)

1.57 (s, -CH₃ at 33 of B₁ and B₂)

2.63 (t, >NCH₂CH₂CH₂CH₃ of B₁ and B₂)

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- 2.65 to 3.30 (mt, $\text{-S-CH}_2\text{CH}_2\text{N<}$, >CH_2 at 15,
 \downarrow
0 -H₄ of B₁ and B₂)
- 3.74 and 3.92 (2d, >CH_2 at 17 of B₁)
- 3.73 and 3.94 (2d, >CH_2 at 17 of B₂)
- 5 4.78 (d, -H₂₇ of B₂)
- 4.75 to 4.90 (mt, -H₁₃ and -H₁₄ of B₁ and B₂)
- 5.27 (d, -H₂₇ of B₁)
- 5.70 (2d, -H₁₁ of B₁ and B₂)
- 7.69 (dd, >NH at 8 of B₂)
- 10 7.79 (dd, >NH at 8 of B₁)
- 7.84 (s, -H₂₀ of B₂)
- 7.85 (s, -H₂₀ of B₁)

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (25 g) and 2-butylaminoethanethiol (6.34 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 12 to 15 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-butylaminoethyl)thiopristinamycin II_B (isomer B) (3.15 g) is obtained in the form of a yellow powder melting at about 110°C. After concentrating fractions 15 to 25 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) (5.89 g) is obtained.

EXAMPLE 18

By using a method similar to that described in

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Example 1, but starting from 26-(2-decylaminoethyl)thio-
pristinamycin II_B (8.6 g), trifluoroacetic acid (0.9 cc)
and meta-chloroperbenzoic acid (2.35 g) and after purifi-
cation by "flash" chromatography [eluent: chloroform-
5 methanol (90-10 by volume)], 40-cc fractions being collec-
ted, and concentrating fractions 12 to 15 to dryness under
reduced pressure (2.7 kPa) at 30°C, 26-(2-decylamino-
ethyl)sulphonylpristinamycin II_B (80% isomer A₂) (1.5 g)
is obtained in the form of a yellow powder melting at
10 about 128°C.

NMR spectrum:

0.88 (t, ¹³-(CH₂)₉-CH₃),
1.30 [m, (¹³>CH₂)₈],
1.50 [m, (¹³>CH₂)₈],
15 1.77 (s, ¹³-CH₃ at 33),
4.81 (d, -H₂₇),
5.51 (d, -H₁₃),
6.19 (d, -H₁₁),
6.53 (mt, >NH at 8),
20 8.13 (s, ¹³-H₂₀).

After concentrating fractions 15 to 19 to dryness
under reduced pressure (2.7 kPa) at 30°C, 26-(2-decyl-
aminoethyl)sulphonylpristinamycin II_B (mixture of isomers)
(2.51 g) is obtained in the form of a yellow powder melt-
25 ing at about 124°C.

NMR spectrum (mixture of isomers: 50% type A₂,
15% A₁, 20% B₁ and 15% B₂),

1.54 (s, -CH₃ at 33 of B₁ and B₂),
3.72 and 3.88 (2d, >CH₂ at 17 of B₁),
3.70 and 3.92 (2d, >CH₂ at 17 of B₂),
4.75 (d, -H₂₇ of B₂),
5.25 (d, -H₂₇ of B₁),
7.67 (dd, >NH at 8 of B₂),
7.77 (dd, >NH at 8 of B₁),
7.81 (s, -H₂₀ of B₁ and B₂),

(characteristic peaks of isomers A₂ and A₁, identical to
those mentioned above and below, respectively).

An aqueous solution containing 1% of 26-(2-decyl-
aminoethyl)sulphonylpristinamycin II_B in the form of

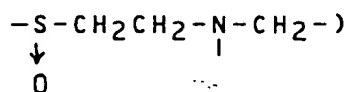
hydrochloride is obtained with:

26-(2-decylaminoethyl)sulphonylpristinamycin II_B ... 15 mg
0.1 N hydrochloric acid 0.2 cc
distilled water q.s. 1.5 cc.

After concentrating fractions 20 to 24 to dryness
under reduced pressure (2.7 kPa) at 30°C, 26-(2-decyl-
aminoethyl)sulphonylpristinamycin II_B (isomers: 60% A₁,
20% A₂, 20% B₁) (1.12 g) is obtained in the form of
a yellow powder melting at about 136°C.

NMR spectrum (isomer A₁):

2.50 to 3.20 (mt, >CH₂ at 15, -H₄ and



3.82 (borderline AB, >CH_2 at 17)

5.27 (d, $-\text{H}_{27}$)

5.46 (d, $-\text{H}_{13}$)

6.15 (d, $-\text{H}_{11}$)

5 6.62 (mt, >NH at 8)

8.12 (s, $-\text{H}_{20}$)

P 26-(2-Decylaminoethyl)thiopristinamycin II_B can be prepared as follows:

P By using a method similar to that described in
10 Example 3, but starting from pristinamycin II_A (5.25 g) and 2-decylaminoethanethiol (3.26 g), and after purification by "flash" chromatography [eluent: methylene chloride-methanol (95-5 by volume)], and concentrating fractions
15 20 to 43 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-decylaminoethyl)thiopristinamycin II_B (1.2 g) is obtained in the form of a yellow powder melting at about 80°C.

P NMR spectrum (70-30 mixture of A and B isomers):

0.88 (t, $-\text{CH}_3$)

20 1.30 }
1.53 } (mt, $-(\text{CH}_2)_8-$)

1.54 (s, $-\text{CH}_3$ at 33 of B)

1.72 (s, $-\text{CH}_3$ at 33 of A)

2.6 to 3 (mt, $-\text{SCH}_2-\text{CH}_2-\text{N}-\text{CH}_2-$)

3.38 (broad d, $-\text{H}_{26}$ of A)

3.50 (mt, $-\text{H}_{26}$ of B)

25

150

4.64 (d, $J = 3.5$, $-H_{27}$ of B)

4.72 (broad s, $-H_{27}$ of A)

7.80 (s, $-H_{20}$ of B)

8.12 (s, $-H_{20}$ of A)

5 EXAMPLE 19

By using a method similar to that described in Example 1, starting from 26-(2-cyclohexylaminoethyl)sulphinypristinamycin II_B (isomers: 80% A, 20% B) (4.4 g), trifluoroacetic acid (0.5 cc) and meta-chloroperbenzoic acid (1.15 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 24 to 29 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-cyclohexylaminoethyl)sulphinypristinamycin II_B (90% isomer A₂) (0.38 g) is obtained in the form of a light-yellow powder melting at about 166°C.

NMR spectrum:

1.05 to 1.35 [mt, cyclohexyl $>CH_2$ (partly)]

1.77 (s, $-CH_3$ at 33)

1.55 to 2.25 [mt, $>CH_2$ at 25, $-H_{29}$ and cyclohexyl $>CH_2$ (partly)]

2.45 to 3.35 (mt, $-H_{26}$, $>CH_2$ at 15, $-H_4$ and $-S-CH_2CH_2N-CH<$)
 \downarrow
 O

3.82 (s, $>CH_2$ at 17)

4.82 (d, $-H_{27}$)

5.52 (d, $-H_{13}$)

101

6.19 (d, -H₁₁)

6.38 (dd, >NH at 8)

8.14 (s, -H₂₀)

26-(2-Cyclohexylaminoethyl)thiopristinamycin II_B

5 can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (5.25 g) and 2-cyclohexylaminoethanethiol (3.6 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (93-7 by volume)] and concentrating fractions 7 to 18 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-cyclohexylaminoethyl)thiopristinamycin II_B (1.7 g) is obtained in the form of a beige powder melting at about 120°C.

15 NMR spectrum:

1 to 1.4 [mt, cyclohexyl >CH₂ (partly)],

1.54 (s, -CH₃ at 33 isomer B),

1.73 (s, -CH₃ at 33 isomer A),

1.6 to 2 [mt, cyclohexyl >CH₂ (partly)],

20 2.80 (mt, >NCH₂-),

2.93 (t, -SCH₂-),

3.36 (broad d, -H₂₆ isomer A),

3.50 (mt, -H₂₆ isomer B),

4.64 (d, J = 3, -H₂₇ isomer B),

25 4.72 (broad s, -H₂₇ isomer A),

6.50 (mt, -NHg isomer A),

7.75 (mt, -NHg isomer B)

7.80 (s, -H₂O isomer B)

8.12 (s, -H₂O isomer A)

2-Cyclohexylaminoethanethiol can be prepared according to the method described by D.D. Reynolds, M.K.

Massad, D.L. Fields and D.L. Johnson, J. Org. Chem. 26, 5109 (1961).

EXAMPLE 20

By using a method similar to that described in Example 2, but starting from 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin II_B (isomers: 80% A, 20% B) (5 g), sodium bicarbonate (1.17 g) and 98% meta-chloroperbenzoic acid (1.2 g), after purification by "flash" chromatography [eluent: dichloromethane-methanol (80-20 by volume)], 30-cc fractions being collected, and concentrating fractions 40 to 60 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (3.5 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 25-cc fractions being collected. After concentrating fractions 11 to 18 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (1.2 g) is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 35°C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)-sulphinypristinamycin II_B (isomer A₂) (1.1 g) is obtained in the form of a yellow powder melting at about 126°C.

P NMR spectrum:

1.10 to 2 (mt, cyclohexyl >CH_2)

1.76 (s, $-\text{CH}_3$ at 33)

2.34 (s, >N-CH_3)

5 2.45 (mt, >N-CH<)

2.7 to 3.15 (mt, $-\text{S-CH}_2\text{-CH}_2\text{N<}$ and $-\text{H}_4$)
 \downarrow
 0

2.93 and 3.14 (2 dd, >CH_2 at 15)

3.25 (ddd, $-\text{H}_{26}$)

10 3.82 (s, >CH_2 at 17)

4.82 (d, $-\text{H}_{27}$)

5.52 (d, $-\text{H}_{13}$)

6.18 (d, $-\text{H}_{11}$)

6.43 (dd, >NH at 8)

15 8.13 (s, $-\text{H}_{20}$)

P 26-(N-Cyclohexyl-N-methyl-2-aminoethyl)thiopris-

tinamycin II_B (isomers: 80% A, 20% B) can be obtained

by a method similar to that described in Example 3 for

the preparation of the starting material, but starting from

20 pristinamycin II_A (10.5 g) and N-cyclohexyl-N-methyl-

2-aminoethanethiol (4 g). After purification by "flash"

chromatography [eluent: ethyl acetate-methanol (80-20 by

volume)], 30-cc fractions being collected, and concentra-

ting fractions 42 to 96 to dryness under reduced pressure

25 (2.7 kPa) at 30°C, a yellow solid is obtained which is

stirred in isopropyl ether (80 cc), separated off by fil-

tration and then dried under reduced pressure (90 Pa) at

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35°C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin II_B (isomers: 80% A and 20% B) (7.9 g) is obtained in the form of a yellow powder melting at about 116°C.

5 NMR spectrum (80/20 mixture of two isomers A and B):

1.25 and 1.6 to 1.9 (mt, cyclohexyl >CH₂ for A and B)

1.56 (s, -CH₃ at 33 of B)

1.73 (s, -CH₃ at 33 of A)

10 2.25 to 2.5 (mt, cyclohexyl >CH- for A and B)

2.32 (s, >N-CH₃ of B)

2.35 (s, >N-CH₃ of A)

2.6 to 2.8 (mt, -H₄ of A and B)

2.78 (borderline AB, -SCH₂CH₂N< of A and B)

15 2.9 and 3.14 (2dd, >CH₂ at 15 of A)

3.41 (broad d, -H₂₆ of A)

3.73 and 3.91 (2d, >CH₂ at 17 of B)

3.83 (s, >CH₂ at 17 of A)

4.65 (d, -H₂₇ of B)

20 4.76 (broad s, -H₂₇ of A)

5.49 (d, -H₁₃ of A)

6.16 (d, -H₁₁ of A)

6.36 (mf, >NH at 8 of A)

7.73 (mf, >NH at 8 of B)

25 7.82 (s, -H₂₀ of B)

8.13 (s, -H₂₀ of A)

N-Cyclohexyl-N-methyl-2-aminoethanethiol can be

obtained as follows:

- P* A 6 N aqueous solution of sodium hydroxide (23 cc) is added under a nitrogen atmosphere to S-(N-cyclohexyl-N-methyl-2-aminoethyl)isothiuronium dihydrochloride (20 g).
- 5 After being stirred at 100°C for 2 hours, the mixture is cooled to 25°C and then a concentrated solution of hydrochloric acid is added to it to a pH of 9. The solution is washed with dichloromethane (3 x 50 cc) and then the organic phases are combined, dried over magnesium
- 10 sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give an oil, which is purified by distillation under reduced pressure (130 Pa). N-Cyclohexyl-N-methyl-2-aminoethanethiol (4.3 g) is obtained in the form of a colourless liquid [b.p. (130 Pa)
- 15 = 68°C]. *8*

P N-Cyclohexyl-N-methyl-2-aminoethanethiuronium dihydrochloride can be obtained as follows:

- P* Thiourea (10.7 g) is added to 2-(N-cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride (30 g) in ethanol
- 20 (300 cc). The solution obtained is heated for 18 hours at 78°C. After cooling, the white solid obtained is filtered off and then washed with ethanol. In this manner, N-cyclohexyl-N-methyl-2-aminoethanethiuronium dihydrochloride (21.5 g) is obtained in the form of a white solid
- 25 melting at 248°C.

P 2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride can be obtained as follows:

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N-Cyclohexyl-N-methyl-2-aminoethanol (25 g) is added dropwise to thionyl chloride (120 cc) and then the mixture is heated for 24 hours at 70°C. After the excess thionyl chloride has been distilled off, the orange oil obtained is stirred into ethyl ether (200 cc) to give a white solid, which is separated off by filtration and then washed with ether. 2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane (30 g) is obtained in the form of a white solid melting at 154°C.

10 EXAMPLE 21

By using a method similar to that described in Example 1, but starting from 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin IIg (isomer A) (4.3 g) trifluoroacetic acid (0.45 cc) and meta-chloroperbenzoic acid (1.2 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 30-cc fractions being collected, and concentrating fractions 42 to 56 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]sulphonylpristinamycin IIg (isomer A₂) (1.2 g) is obtained in the form of a light-yellow powder melting at about 135°C.

NMR spectrum:

1.78 (s, -CH₃ at 33)

25 2.32 (s, >N-CH₃)

2.42 (m, -CO-N $\begin{array}{c} \text{CH}_2 \\ \text{CH}_2 \end{array}$ -N-)

2.95 to 3.28 (mt, $-\text{S}-\text{CH}_2-$)



3.54 (m, $-\text{CO}-\text{N} \begin{array}{c} \text{CH}_2 \\ \text{CH}_2 \end{array} \text{N}-$)

5 3.82 (s, $>\text{CH}_2$ at 17)

4.58 (mt, $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}<$)

4.82 (d, $-\text{H}_{27}$)

5.50 (d, $-\text{H}_{13}$)

10 6.20 (d, $-\text{H}_{11}$)

6.39 (dd, $>\text{NH}$ at 8)

8.14 (s, $-\text{H}_2\text{O}$)

After concentrating fractions 65 to 95 to dryness under reduced pressure (2.7 kPa) at 30°C , 26-[(4-methyl-1-piperazinyl)-2-carboxyloxyethyl]sulphonylpristinamycin IIg (isomer A₁) (0.65 g) is obtained in the form of a light-yellow powder melting at about 140°C .

NMR spectrum:

1.75 (s, $-\text{CH}_3$ at 33)

20 2.34 (s, $>\text{N}-\text{CH}_3$)

2.44 (m, $-\text{CO}-\text{N} \begin{array}{c} \text{CH}_2 \\ \text{CH}_2 \end{array} \text{N}-$)

2.90 to 3.15 (mt, $-\text{S}-\text{CH}_2-$)



25 3.55 (m, $-\text{CO}-\text{N} \begin{array}{c} \text{CH}_2 \\ \text{CH}_2 \end{array} \text{N}-$)

3.83 (s, $>\text{CH}_2$ at 17)

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4.51 to 4.65 (2ddd, $-\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}<$)

5.28 (d, $-\text{H}_{27}$)

6.19 (d, $-\text{H}_{11}$)

5 6.55 (dd, $>\text{NH}$ at 8)

8.14 (s, $-\text{H}_{20}$)

26-[(4-Methyl-1-piperazinyl)-2-carboxyloxyethyl] thiopristinamycin IIg can be prepared as follows:

10 By using a method similar to that described in Example 3, starting from pristinamycin IIA (5.25 g) and (4-methyl-1-piperazinyl)-2-carboxyloxyethanethiol (3.76 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 10 to 18 to dryness under reduced pressure

15 (2.7 kPa) at 30°C, 26-[(4-methyl-1-piperazinyl)-2-carboxyloxyethyl]thiopristinamycin IIg is obtained in the form of a beige powder melting at about 100°C.

NMR spectrum:

1.54 (s, $-\text{CH}_3$ at 33 of isomer B)

20 1.73 (s, $-\text{CH}_3$ at 33 of isomer A)

2.3 (s, $>\text{N}-\text{CH}_3$)

2.4 (m, $\begin{array}{c} -\text{CH}_2- \\ -\text{CH}_2- \end{array} \text{N}-$)

3.55 (m, $-\text{OOC}-\text{N} \begin{array}{c} \text{CH}_2- \\ \text{CH}_2- \end{array}$)

3.98 (mt, $-\text{CH}_2-\text{OCO}-$)

25

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4.59 (d, $J = 4$, $-H_{27}$ of isomer B)

4.69 (broad s, $-H_{27}$ of isomer A)

7.05 (t, $>NH$ at 8 of isomer A)

7.7 (m, $>NH$ at 8 of isomer B)

5 7.80 (s, $-H_{20}$ of isomer B)

8.10 (s, $-H_{20}$ of isomer A)

P (4-Methyl-1-piperazinyl)-2-carbonyloxyethanethiol

can be prepared according to the method described by D.D.

Reynolds, D.L. Fields and D.L. Johnson, J. Org. Chem. 26,

10 5111 (1961).

EXAMPLE 22

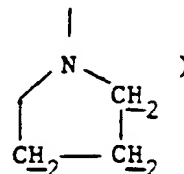
By using a method similar to that described in Example 1, but starting from 26-[(S)-1-methyl-2-pyrrolidinyl]methylthiopristinamycin IIB (isomer A) (7.8 g),
 15 trifluoroacetic acid (0.91 cc) and meta-chloroperbenzoic acid (2.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 26 to 36 to dryness under reduced pressure (2.7 kPa)
 20 at 30°C, 26-[(S)-1-methyl-2-pyrrolidinyl]methylsulphinypristinamycin IIB (isomer A₂) (2.3 g) is obtained in the form of a light-yellow powder melting at about 140°C.

NMR spectrum:

1.76 (s, $-CH_3$ at 33)

2.48 (s, $>NCH_3$)

1.70 to 2.60 (mt, $-H_{29}$ and $>CH_2$ at 25 and



25

2.75 to 3.25 (mt, $-\text{S}-\text{CH}_2-\text{CH}<$)
 \downarrow
 0

3.82 (s, $>\text{CH}_2$ at 17)

4.81 (d, $-\text{H}_{27}$)

5 5.52 (d, $-\text{H}_{13}$)

6.20 (d, $-\text{H}_{11}$)

6.42 (dd, $>\text{NH}$ at 8)

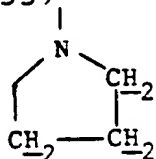
8.14 (s, $-\text{H}_{20}$)

After concentrating fractions 46 to 59 to dryness
 10 under reduced pressure (2.7 kPa) at 30°C , 26-[(S)-1-
 methyl-2-pyrrolidinyl]methylsulphonylpristinamycin IIg
 (isomer A₁) (1.1 g) is obtained in the form of a light-
 yellow powder melting at about 148°C .

NMR spectrum:

15 1.73 (s, $-\text{CH}_3$ at 33)

1.70 to 2.50 (mt, $-\text{H}_{29}$)



2.41 (s, $>\text{NCH}_3$)

2.65 to 3.25 (mt, $>\text{CH}_2$ at 15, $-\text{H}$ at 4, $-\text{S}-\text{CH}_2-\text{CH}<$)
 \downarrow
 0

3.82 (borderline AB, $>\text{CH}_2$ at 17)

5.45 (d, $-\text{H}_{13}$)

6.17 (d, $-\text{H}_{11}$)

8.11 (s, $-\text{H}_{20}$)

25 26-(1-Methyl-2-pyrrolidinyl)methylthiopristina-
 mycin IIg can be prepared as follows:

By using a method similar to that described in

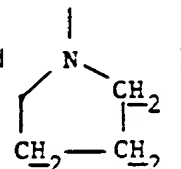
Example 3, but starting from pristinamycin II_A (10.5 g) and [(S)-1-methyl-2-pyrrolidinyl]methanethiol (3.14 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 20 to 35 to dryness under reduced pressure (2.7 kPa) at 30°C, the A isomer (7.8 g) is obtained in the form of a yellow powder melting at approximately 120°C.

NMR spectrum:

1.70 (s, -CH₃ at 33)

2.38 (s, >N-CH₃)

1.70 to 2.50 (mt, -H₂₉, >CH₂ at 25 and



2.6 to 3.20 (mt, -S-CH₂-CH<)

3.82 (s, >CH₂ at 17)

4.73 (d, -H₂₇)

5.45 (d, -H₁₃)

6.15 (d, -H₁₁)

6.41 (dd, >NH at 8)

8.11 (s, -H₂₀)

A 4 N aqueous solution of sodium hydroxide (100 cc) is added to crude S-[(S)-1-methyl-2-pyrrolidinylmethyl]-isothiuronium dihydrochloride (25 g) dissolved in distilled water (100 cc), and then the mixture is stirred for 2 hours at 90°C under a nitrogen atmosphere. The reaction mixture is cooled to 0°C, a 12 N aqueous solution of hydrochloric acid (25 cc) is added to it, and then it is extracted with methylene chloride (2 x 200 cc).

The organic phase is dried over sodium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. In this manner [(S)-1-methyl-2-pyrrolidinyl]methanethiol (5.9 g) is obtained in the form of a light-yellow oil, which is used in the subsequent reaction without additional purification.

$R_f = 0.15$; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

Thiourea (10.7 g) is added to [(S)-1-methyl-2-pyrrolidinyl]chloromethane hydrochloride (11.9 g) dissolved in ethanol (50 cc), and then the mixture is stirred for 48 hours under reflux. The mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The residue is taken up again with hot ethanol (100 cc) and then filtered through activated plant charcoal. After the filtrate has been concentrated to dryness under reduced pressure (2.7 kPa) at 40°C, a light-yellow oil (25 g) consisting of S-[(S)-1-methyl-2-pyrrolidinylmethyl]isothiuronium dihydrochloride and excess thiourea, is obtained.

$R_f = 0.1$; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

[(S)-1-Methyl-2-pyrrolidinyl]chloromethane hydrochloride can be prepared according to the method described by T. Hayashi et al., J. Org. Chem., 48, 2195 (1983).

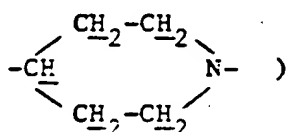
EXAMPLE 23

By using a method similar to that described in

Example 1, but starting from 26-(1-methyl-4-piperidinyl)-thiopristinamycin II_B (2.6 g), trifluoroacetic acid (0.3 cc) and meta-chloroperbenzoic acid (0.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 20 to 35 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(1-methyl-4-piperidinyl)sulphonylpristinamycin II_B (isomer A₂) (0.33 g) is obtained in the form of a yellow powder melting at about 170°C.

NMR spectrum:

1.76 (s, -CH₃ at 33)

2.2 to 3.00 (mt, )

2.32 (s, >N-CH₃)

3.82 (s, >CH₂ at 17)

4.85 (d, -H₂₇)

5.50 (d, -H₁₃)

6.19 (d, -H₁₁)

6.37 (dd, >NH at 8)

8.15 (s, -H₂₀)

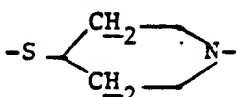
26-(1-Methyl-4-piperidinyl)thiopristinamycin II_B can be obtained as follows:


By using a method similar to that described in Example 3, but starting from pristinamycin II_A (3.15 g) and 2-methyl-4-piperidinethiol (1.6 g), and adding

triethylamine (0.6 g) to the reaction mixture, and after purification by "flash" chromatography [eluent: methylene chloride-methanol (92-8 by volume)], and concentrating fractions 4 to 20 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(1-methyl-4-piperidinyl)thiopristinamycin IIg (0.9 g) is obtained in the form of a yellow powder melting at about 180°C.

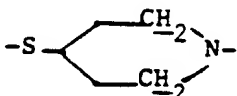
NMR spectrum:

10

2.10 (m, 4H : -S--)

2.25 (s, 3H : -S--)

15

2.80 (m, 4H : -S--)

3.55 (m, 1H : -H₂₆)

4.62 (m, 1H : -H₂₇)

7.70 (m, 1H : -H₈)

8.10 (s, 1H : -H₂₀)

20

2-Methyl-4-piperidinethiol can be prepared by the method described by H. Barrer and R.E. Lyle, J. Org. Chem., 27, 641 (1962) .

EXAMPLE 24

Trifluoroacetic acid (0.92 cc) is added under a nitrogen atmosphere to 26-(2-diethylaminoethyl)thiopristinamycin IIg (7.8 g) dissolved in methanol (60 cc), at 0°C. After 15 minutes at 0°C, the temperature is raised

to 15°C and then selenium dioxide (1.37 g) is added. When all the selenium dioxide has dissolved, a 30% strength aqueous solution of hydrogen peroxide (7 cc) is added slowly at a temperature below 25°C. After being stirred at 25°C for 1 hour, the reaction mixture is cooled to 10°C, a saturated aqueous solution of sodium bicarbonate (50 cc) is added to it, and then it is extracted with methylene chloride (4 x 50 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The yellow solid obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected. After concentrating fractions 31 to 38 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid is obtained, which is purified by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected. After concentrating fractions 27 to 33 to dryness under reduced pressure, a white solid is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30°C. In this manner, 26-(2-diethylaminoethyl)sulphonylpristinamycin II_B (isomer A) (0.5 g) is obtained in the form of a white solid melting at about 150°C.

25

NMR spectrum:

0.97 (d, -CH₃ at 30 and 31 and ethyl -CH₃)

1.75 (s, -CH₃ at 33)

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2.62 (q, $-\text{N} \begin{array}{l} \text{CH}_2^- \\ \text{CH}_2^- \end{array}$)

3.00 to 3.40 (mt, $-\text{SO}_2\text{CH}_2\text{CH}_2\text{N} <$)

3.82 (s, $>\text{CH}_2$ at 17)

5 5.34 (d, $-\text{H}_{13}$)

5.43 (d, $-\text{H}_{13}$)

6.16 (d, $-\text{H}_{11}$)

6.54 (dd, $>\text{NH}$ at 8)

8.10 (s, $-\text{H}_2\text{O}$)

10 EXAMPLE 25

A method similar to that described in Example 24 is used, but starting from 26-(2-diisopropylaminoethyl)-thiopristinamycin IIg (isomer A) (6.86 g), trifluoroacetic acid (0.77 cc), selenium dioxide (1.15 g), and a 30% strength aqueous solution of hydrogen peroxide (6.33 cc). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected, and concentrating fractions 28 to 31 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (0.7 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (85-15 by volume)], 30-cc fractions being collected. After concentrating fractions 26 to 33 to dryness under reduced pressure, a yellow solid is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30°C.

26-(2-Diisopropylaminoethyl)sulphonylpristinamycin II_B
(isomer A) (0.6 g) is obtained in the form of a light-
yellow solid melting at about 140°C.

NMR spectrum:

1.06 (d, isopropyl -CH₃)

1.75 (s, -CH₃ at 33)

2.79 (mt, -H₄)

2.92 and 3.10 (2dd, $\geq\text{CH}_2$ at 15)

2.7 at 3.30 (mt, -S-CH₂CH₂N(CH₃)₂)

3.52 (broad d, -H₂6)

3.82 (s, $\geq \text{CH}_2$ at 17)

5.27 (fine d, -H₂₇)

5.47 (d, $-H_{13}$)

6.17 (d, -H₁₁)

6.42 (mt, >NH at 8)

8.12 (s, -H₂O)

REFERENCE EXAMPLE 1

Pristinamycin I_A (0.5 g) and sodium cyanoboro-
hydride (20 mg) are added to a solution of 3-dimethyl-
aminopropylamine (0.41 cc) in methanol (15 cc) containing
a 2 N methanolic solution (2.4 cc) of hydrogen chloride
gas, maintained at 55°C. The solution obtained is then
allowed to regain a temperature of about 20°C over approx-
imately 2 hours, and it is then concentrated to dry-
ness under reduced pressure (2.7 kPa) at 30°C. The resi-
due obtained is triturated with a mixture of methylene

chloride (50 cc) and of a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (20 cc in total). The organic phases
5 are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (80-20 by volume)]. Fractions 15 to 30 are combined and
10 concentrated to dryness under reduced pressure (2.7 kPa) at 30°C; the residue obtained is triturated with ethyl ether (5 cc), filtered off and dried under reduced pressure (0.027 kPa) at 20°C. In this manner 5 γ -deoxy-(3-dimethylaminopropyl)-5 γ -aminopristinamycin I_A (60 mg)
15 is obtained in the form of a cream-coloured powder melting at about 160°C.

The complete NMR spectrum shows the following characteristics:

δ (ppm)	Form of signal	Attribution
8.40	d	6 NH
8.25	d	1 NH
7.55	dd	H ₆
7.05	m	6 γ + 6 δ + 6 ϵ
7	dd	H ₄
6.90	dd	H ₅
6.70	d	} 4 δ + 4 ϵ
6.40	d	
6.50	d	
5.75	ddd	2 NH
5.45	d	1 β
5.25	dd	6 α
5	s (broad)	4 α
4.75	dd	5 α
4.60	m	1 α
4.45	(d broad)	2 α
4.40	dd	5 ϵ_1
3.4	dd broad)	3 α
3.20	dd broad)	3 δ_1
3	s	3 δ_2
3	m	4 CH ₃
2.80	s	5 γ + 4 β_1 and 2
2.65	t	4 N(CH ₃) ₂
2.35	m	-NCH ₂ - (chain)
2.25	t	5 ϵ_2 + 5 β_1
2.20	s	-NCH ₂ - (chain)
1.60	m	-N(CH ₃) ₂ (chain)
1.25	d	-CH ₂ - (chain) 2 β + 3 γ
0.90	t	1 γ
0.50	dddd	2 γ
		5 β_2

An aqueous solution at a concentration of 10% of 5Y-deoxy-(3-dimethylaminopropyl)-5Y-amino-pristinamycin 1A (product A), in the form of hydrochloride, is obtained

with:

5 product A..... 0.1 g
2 N hydrochloric acid 0.52 cc
distilled waterq.s..... 1 cc

By using a method similar to that described in the reference Example 1, the following synergists of general formula (V), which can be combined with the products according to the invention, are prepared:

[The symbols \oplus Z and R₁ are defined as at 1) for the general formula (V)].

Reference example	Y	X	1) Melting point 2) Solubility
2	$-N(CH_3)_2$	$-NH(CH_2)_2N(CH_3)_2$	1) Yellow powder M. abt. 180°C 2) 10% aqueous solution of hydrochloride
3	$-N(CH_3)_2$	$-N \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} N-CH_3$	1) White powder M. abt. 195°C 2) 10% aqueous solution of hydrochloride
4	$-N(CH_3)_2$	$-NH- \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} N-CH_3$	1) Beige powder M. abt. 195°C 2) 3.7% aqueous solution of hydrochloride
5	$-N(CH_3)_2$	$-NHOH$	1) White powder M. abt. 170°C 2) 10% aqueous solution of hydrochloride
6	$-N(CH_3)_2$	$-NH(CH_2)_3OH$	1) Cream powder M. abt. 160°C 2) 2% aqueous solution of hydrochloride
7	$-H$	$-NH(CH_2)_3N(CH_3)_2$	1) Beige powder M. abt. 140°C 2) 10% aqueous solution of hydrochloride

REFERENCE EXAMPLE 8

A 5 N ethanolic solution (2.8 cc) of dimethylamine, followed by a 5 N methanolic solution (2 cc) of hydrogen chloride gas are added to a solution of pristinamycin I_A (2 g) in methanol (25 cc). Sodium cyanoborohydride (76 mg) are added to the solution thus obtained, and the mixture is then stirred at a temperature of about 20°C for 48 hours. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is triturated with a mixture of methylene chloride (25 cc) and of a saturated aqueous solution of sodium bicarbonate (25 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (92-8 by volume)]. Fractions 5 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. In this manner 5 γ -deoxy-5 γ -dimethylaminopristinamycin I_A (0.7 g) is obtained in the form of a beige powder melting at about 170°C.

NMR spectrum:

0.70 (dt, 1H : 5 β 2)
2.10 to 2.60 (m, 4H : 5 δ ₁ + 5 δ ₂ + 5 β ₁ + 5 γ)
2.15 (s, 3H X 0.8 : -N(CH₃)₂ 1st isomer)
2.20 (s, 3H X 0.2 : -N(CH₃)₂ 2nd isomer)

An aqueous solution at a concentration of 2% of 5 δ -deoxy-5 δ -dimethylaminopristinamycin I_A (product B), in the form of hydrochloride, is obtained with:

5 *123rd*
product B 0.05 g
0.1 N hydrochloric acid 0.56 cc
distilled water q.s. 2.5 cc

REFERENCE EXAMPLE 9

10 By using a method similar to that described in reference Example 8, 5 δ -deoxy-5 δ -methylaminopristinamycin I_A (0.35 g) is obtained in the form of a yellow powder melting at about 185°C.

An aqueous solution at a concentration of 1% of 5 δ -deoxy-5 δ -methylaminopristinamycin I_A, in the form of hydrochloride, is obtained.

15 REFERENCE EXAMPLE 10

By using a method similar to that described in reference Example 8, 5 δ -deoxy-5 δ -[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin I_A is obtained in the form of a white powder melting at about 120°C.

20 An aqueous solution at a concentration of 10% of 5 δ -deoxy-5 δ -[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin I_A (product D), in the form of hydrochloride, is obtained.

Anti REFERENCE EXAMPLE 11

25 A 3- \AA molecular sieve (5 g) is added to a solution of pristinamycin I_A (3 g), 4-diethylamino-2-methylbutylamine (3.3 g), sodium cyanoborohydride (0.11 g) and a 5 N

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methanolic solution (9 cc) of hydrogen chloride gas in methanol (75 cc). The suspension obtained is stirred at a temperature of about 20°C for 4 days, and is then filtered; the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is triturated with a mixture of methylene chloride (50 cc) and a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]. In this manner, 5'-deoxy-15 5'-(4-diethylamino-2-methylbutyl)aminopristinamycin I_A (0.7 g) is obtained in the form of a beige powder melting at about 160°C.

NMR spectrum:

1.10 (mt, 9H : -N(CH₂CH₃)₂ + -CH-CH₃)
ca 1.7 (m, 4H : -CH₂-CH₂-CH₂-N(C₂H₅)₂)
2.90 (m, 6H : -CH₂N(CH₂CH₃)₂)
7.70 (mt, 1H X 0.45 : 1'H₆ 1st isomer)
7.77 (mt, 1H X 0.55 : 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 10% of 5'-deoxy-5'-(4-diethylamino-2-methylbutyl)aminopristinamycin I_A (product F) in the form of hydrochloride, is obtained with:

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12807
product F 0.1 g

0.1 N hydrochloric acid q.s. 1 cc

REFERENCE EXAMPLE 12

Sodium cyanoborohydride (0.7 g) is added to a
5 solution of 5 γ -deoxy-5 γ -hydroxyiminopristinamycin I_A
(12.5 g) in methanol (300 cc) containing a 2 N methanolic
solution (10 cc) of hydrogen chloride gas. The solution
obtained is stirred at a temperature of about 20°C for
2 days, and is then concentrated to dryness under reduced
10 pressure (2.7 kPa) at 30°C. The residue is triturated
in a mixture of methylene chloride (200 cc) and a satu-
rated aqueous solution of sodium bicarbonate (100 cc); the
organic phase is separated off and the aqueous phase is
extracted with methylene chloride (100 cc). The organic
15 phases are combined, dried over magnesium sulphate, fil-
tered, and concentrated to dryness under reduced pressure
(2.7 kPa) at 30°C. After purification by "flash" chroma-
tography [eluent: chloroform-methanol (95-5 by volume)],
5 γ -deoxy-5 γ -hydroxyaminopristinamycin I_A (6.8 g) is
20 obtained in the form of a white powder melting at about
170°C.

NMR spectrum:

0.4 (m, 1H : 5B₂),

2.45 (d, 1H : 5B₁),

3.1 (d : 5 γ in complex unresolved bands),

7.80 (mt, 1H X 0.75 : 1'H₆ 1st isomer),

7.95 (mt, 1H X 0.25 : 1'H₆ 2nd isomer) ✓

P 5 β -Deoxy-5 β -hydroxyiminopristinamycin I_A can be obtained by stirring pristinamycin I_A (15 g) and hydroxylamine hydrochloride (7.5 g) dissolved in methanol (150 cc) containing a 2 N methanolic solution (8 cc) of hydrogen chloride gas for 5 hours at a temperature of about 20°C. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is triturated with a mixture of chloroform (100 cc) and of a saturated aqueous solution of sodium bicarbonate (100 cc); the organic phase is separated off and the aqueous phase is extracted twice with chloroform (200 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. In this manner, 5 β -deoxy-5 β -hydroxyiminopristinamycin I_A (14 g) is obtained in the form of a beige powder melting at 210°C.

NMR spectrum:

0.35 (dd, 1H : 5 β 2)

3.25 (m, 2H : 4E2 + 5 β 1)

5.05 (d, 1H : 5 α)

5.5 (m, 2H including 5E1)

7.80 (dd, 1H X 0.40 : 1'H₆ 1st isomer)

7.90 (dd, 1H X 0.60 : 1'H₆ 2nd isomer)

REFERENCE EXAMPLE 13

25 P By using a method similar to that described in reference Example 11, 5 β -[N-(carboxymethyl)methylamino]-5 β -deoxypristinamycin I_A (0.8 g) is obtained in the form

of a cream-coloured powder melting at about 140°C.

An aqueous solution at a concentration of 2% of 5X-[N-(carboxymethyl)methylamino]-5X-deoxypristinamycin I_A (product K) is obtained with:

5 product K 0.2 g
distilled water ... q.s. 10 cc

REFERENCE EXAMPLE 14

Acetyl chloride (0.3 cc) is added to a solution of 5Y-deoxy-5Y-(2-dimethylaminoethyl)aminopristinamycin I_A (3.2 g) in chloroform (50 cc) containing triethylamine (0.6 cc). The reaction mixture is stirred at a temperature of about 20°C for 30 minutes and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is purified by "flash" chromatography [eluent: 15 chloroform-methanol (90-10 by volume)]; by concentrating fractions 10 to 21 to dryness under reduced pressure (2.7 kPa) at 30°C, 5X-deoxy-5X-[N-(2-dimethylaminoethyl)-acetamido]pristinamycin I_A (1.8 g) is obtained in the form of a white powder melting at about 170°C.

20 NMR spectrum:

0.9 (m, 4H : 2X + 5β₂)
2.05 to 2.15 (m, 3H : 5δ₁ + 5δ₂ + 5X)
2.15 (s, 3H : -COCH₃)
2.45 (s, 6H : -N(CH₃)₂)
2.35 to 2.60 (m, 5H : >N-CH₂-CH₂-N< + 5β₁)
7.8 (mt, 1H X 0.75 : 1'H₆ 1st isomer)
8.25 (mt, 1H X 0.25 : 1'H₆ 2nd isomer)

P An aqueous solution at a concentration of 10% of 5 γ -deoxy-5 γ -[N-(2-dimethylaminoethyl)acetamido]pristinamycin I_A (product L), in the form of hydrochloride, is obtained with:

5 *12801* product L 0.1 g
0.2 N hydrochloric acid 0.51 cc
distilled water ... q.s. 1 cc
P 5 γ -Deoxy-5 γ -(2-dimethylaminoethyl)aminopristinamycin I_A can be prepared as described in Reference

10 Example 2.

CLYK REFERENCE EXAMPLE 15

P By using a method similar to that described in Reference Example 14, 5 γ -deoxy-5 γ -[N-(3-dimethylaminopropyl)acetamido]pristinamycin I_A (1.6 g) is obtained
15 in the form of an ochre powder melting at 210°C.

An aqueous solution at a concentration of 10% of 5 γ -deoxy-5 γ -[N-(3-dimethylaminopropyl)acetamido]pristinamycin I_A (product M), in the form of hydrochloride, is obtained.

CLYK 20 REFERENCE EXAMPLE 16

P 3-Dimethylaminopropanethiol (1.95 g) is added to a solution of 5 δ -methylenepristinamycin I_A (3.6 g) in a mixture of methanol (25 cc) and chloroform (5 cc), and then the solution obtained is stirred at a temperature of
25 about 20°C for 20 hours. The reaction mixture is then poured into distilled water (250 cc); the emulsion obtained is extracted 3 times with methylene chloride (250 cc in

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total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is purified by "flash" chromatography
5 [eluent: chloroform-methanol (95-5 by volume)]; fractions 10 to 38 are concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is triturated in ethyl ether (30 cc); the crystals obtained are separated off by filtration, and then dried under reduced
10 pressure (27 Pa) at 20°C. In this manner, 58-(3-dimethylaminopropyl)thiomethylpristinamycin I_A is obtained in the form of white crystals melting at 234°C.

NMR spectrum:

δ (ppm)	Form	Attribution
11.65	s (broad)	OH
8.70	d	6 NH
8.40	d	1 NH
7.80	dd	1 H ₆
7.45	m	1 H ₄ + 1 H ₅
7.27	m	6 γ + 6 δ + 6 ϵ
7.17	m	
7.05	d	4 δ + 4 ϵ
6.60	d	
6.47	d	2 >NH
5.87	ddd	1 β
5.83	d	6 α
5.24	m	5 α + 4 α
5.03	ddd	5 ϵ_1
4.85	dd	1 α
4.80	m	2 α
4.53	dd	3 α
3.53	m	3 δ_1
3.35	dd	-CH ₂ -S-SCH ₂ -
3.15	dd	
3.25	s	4 >NCH ₃
3.25	m	3 δ_2
2.90	s	4 -N(CH ₃) ₂
2.90	m	4 β
2.55	t	-CH ₂ N(CH ₃) ₂
2.50	dd	5 ϵ_2
2.40	t	-CH ₂ SCH ₂ -
2.40 to 2.20	m	5 δ + 5 β_1
2.25	s	-CH ₂ N(CH ₃) ₂

T1300t

δ (ppm)	Form	Attribution
2	m	$3\beta_1$
1.75	m	$-\text{SCH}_2\text{CH}_2\text{CH}_2-$
1.8 to 1.45	m	$2\beta_1 + 2\beta_2 + 3\gamma_1$
1.30	d	1γ
1.25 to 1.05	m	$3\gamma_2 + 3\beta_2$
0.9	t	2γ
0.60	dd	$5\beta_2$

5

An aqueous solution at a concentration of 10% of 5 δ -(3-dimethylaminopropyl)thiomethylpristinamycin I_A

(product AA) is obtained with:

product AA 30 mg

0.1 N hydrochloric acid ... q.s. 0.3 cc

5 δ -methylenepristinamycin I_A can be prepared as follows:

Sodium cyanoborohydride (0.43 g) is added to a solution of 5 δ -dimethylaminomethylenepristinamycin I_A

(12 g) in tetrahydrofuran (230 cc) containing trifluoroacetic acid (1.2 cc). The solution obtained is stirred

at a temperature of about 20°C for 4 hours and is then concentrated to dryness under reduced pressure (2.7 kPa)

at 30°C. The residue obtained is purified by "flash"

chromatography [eluent: chloroform-methanol (95-5 by

volume)]; fractions 4 to 15 are concentrated to dryness

under reduced pressure (2.7 kPa) at 30°C. In this manner

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5 δ -methylenepristinamycin I_A (5.5 g) is obtained in the form of white crystals melting at 245°C.

NMR spectrum:

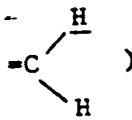
0.55 (d, 1H : 5 β ₂)

2.40 (d, 1H : 5 β ₁)

3.55 (dd, 1H : 5 ϵ ₂)

5.25 (m, 2H : 5 α + 5 ϵ ₁)

5.30 and 6.10 (2s, 2H :



7.85 (dd, 1H : 1'H₆)

10

5 δ -Dimethylaminomethylenepristinamycin I_A can be prepared as follows:

tert-Butoxybis(dimethylamino)methane (230 cc) is added to a solution of pristinamycin I_A (46 g) in 1,2-dichloroethane (460 cc); the solution obtained is stirred at a temperature of about 20°C for 18 hours. The reaction mixture is diluted with methylene chloride (1 litre) and then washed 3 times with a 0.4% strength aqueous solution of ammonium chloride (3 litres in total). The organic phase is dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is triturated with distilled water (600 cc); the mixture is filtered and the solid product is dried under reduced pressure (2.7 kPa) at 20°C. Crude 5 δ -dimethylaminomethylenepristinamycin I_A (41 g) is obtained in the form of a beige powder. This product is of an adequate quality to be used as such in the subsequent steps. It can, however, be

purified as follows:

Crude 5 δ -dimethylaminomethylenepristinamycin 1A (23.5 g) is purified by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)]. Fractions 16 to 5 25 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30 $^{\circ}$ C. In this manner, 5 δ -dimethylaminomethylenepristinamycin 1A (12 g) is obtained in the form of a beige powder melting at about 195 $^{\circ}$ C.

NMR spectrum:

10 0.9 (t, 3H : 2 γ)
1.0 (dd, 1H : 5 β 2)
2.50 (d, 1H, 5 β 1)
3.10 (s, 6H : -N(CH₃)₂)
3.70 (d, 1H : 5 ϵ 2)
15 5.50 (d, 1H : 5 ϵ 1)
7.40 (s, 1H : =CHN(CH₃)₂)
7.75 (dd, 1H : 1'H₆)

REFERENCE EXAMPLE 17

By using a method similar to that described in Reference Example 16, but starting from 5 δ -methylenevirginiamycin S (0.9 g) and 3-dimethylaminopropanethiol (0.52 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 13 to 25 to dryness under reduced pressure (2.7 kPa) at 30 $^{\circ}$ C, 5 δ -(3-dimethylaminopropyl)-thiomethylvirginiamycin S (0.3 g) is obtained in the form of a white powder melting at about 142 $^{\circ}$ C.

NMR spectrum:

0.45 (dd, 1H : $5\beta_2$)

1.90 (m, 2H : $-\text{SCH}_2\text{CH}_2\text{CH}_2\text{N}<$)

2.40 (s, 6H : $-\text{CH}_2-\text{N}<\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$)

2.60 (m, 4H : $-\text{S}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}<$)

3.45 (d, 1H : $5E_2$)

4.85 (m, 3H including $5E_1$)

5.25 (dd, 1H : 5α)

7.78 (dd, 1H : $1'H_6$)

An aqueous solution at a concentration of 10% of 5δ -(3-dimethylaminopropyl)thiomethylvirginiamycin S (product AB), in the form of hydrochloride, is obtained

with:

product AB 0.1 g

hydrochloric acid ... q.s. 1 cc

5δ -Methylenevirginiamycin S can be prepared by a method similar to that described in Reference Example 16

for 5δ -methylenepristinamycin I_A, but starting from

5δ -dimethylaminomethylenevirginiamycin S (2 g) and sodium cyanoborohydride (74 mg). After purification by "flash"

chromatography [eluent: chloroform-methanol (98-2 by volume)] and concentrating fractions 2 to 5 to dryness

under reduced pressure (2.7 kPa) at 30°C, 5δ -methylenevirginiamycin S (1 g) is obtained in the form of a beige powder melting at about 190°C.

NMR spectrum:

0.35 (dd, 1H : $5\beta_2$)
 2.45 (dd, 1H : $5\beta_1$)
 3.55 (dd, 1H : $5\epsilon_2$)
 5.25 (dd, 1H : $5\epsilon_1$)
 5.25 (m, 1H : 5α)
 5.30 and 6.15 (2s, 2H : $=C \begin{smallmatrix} H \\ H \end{smallmatrix}$)
 7.75 (dd, 1 : $1'H_6$)

58-Dimethylaminomethylenevirginiamycin S can be
 10 obtained by using a method similar to that described in
 Reference Example 16 for 58-dimethylaminomethylenepristinamycin I_A, but starting from virginiamycin S (2 g) and
 bis(dimethylamino)tert-butoxymethane (10 cc) and, after purification by "flash" chromatography [eluent: chloroform-
 15 methanol (98-2 by volume)] and concentrating fractions 9
 to 12 to dryness under reduced pressure (2.7 kPa) at 30°C,
 58-dimethylaminomethylenevirginiamycin S (0.8 g) is ob-
 20 tained in the form of a yellow powder melting at about
 175°C.

NMR spectrum:

0.9 (m, 4H : $2\gamma + 5\beta_2$)
 3.05 (s, 6H : $=CH-N(CH_3)_2$)
 3.65 (d, 1H : $5\epsilon_2$)
 4.85 (d, 1H : $5\epsilon_1$)
 5.15 (dd, 1H : 5α)
 7.10 to 7.40 (m : aromatics + $=CH-N$)
 7.70 (dd, 1H : $1'H_6$)

REFERENCE EXAMPLE 18

By using a method similar to that described in Reference Example 16, but starting from 5 δ -methylenepristinamycin I_A (6 g) and 2-(4-methylpiperazinyl)ethanethiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (97-3 by volume)], and concentrating fractions 8 to 20 to dryness under reduced pressure (2.7 kPa) at 30°C, 5 δ -[2-(4-methylpiperazinyl)ethyl]thiomethylpristinamycin I_A (2.6 g) is obtained in the form of white crystals melting at 216°C.

NMR spectrum:

0.60 (dd, 1H : 5 β ₂)

2.27 (s, 3H : >N-CH₃)

2.40 to 2.80 (m, 11H : -CH₂-N $\begin{matrix} \text{CH}_2\text{-CH}_2 \\ \text{CH}_2\text{-CH}_2 \end{matrix}$ -N- + 5 β ₁)

5.05 (dd, 1H : 5 ϵ ₁)

5.27 (m, 2H : 5 α + 4 α)

7.85 (mt, 1H X 0.8 : 1'H₆ 1st isomer)

7.95 (mt, 1H X 0.2 : 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 5% of

5 δ -[2-(4-methyl-1-piperazinyl)ethyl]thiomethylpristinamycin I_A (product AC), in the form of hydrochloride, is obtained with:

product AC	0.1 g
0.1 N hydrochloric acid	0.96 cc
distilled water .. q.s.	2 cc

REFERENCE EXAMPLE 19

By using a method similar to that described in reference Example 16, but starting from 5 δ -methylenepristinamycin 1_A (2 g) and 3-(4-methyl-1-piperazinyl)propane-
 5 thiol (3 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 10 to 25 to dryness under reduced pressure (2.7 kPa) at 30^oc, 5 δ -[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin 1_A (1.9 g) is
 10 obtained in the form of a white powder melting at about 156^oc.

NMR spectrum:

0.65 (dd, 1H : 5 β ₂)

2.30 (s, 3H : >N-CH₃)

2.50 (m, 13H : $-\text{CH}_2\text{N} \begin{matrix} \text{CH}_2\text{CH}_2 \\ \text{CH}_2\text{CH}_2 \end{matrix} \text{N}- + -\text{SCH}_2- + 5\beta_1$)

5.27 (m, 2H : 5 α + 4 α)

7.85 (dd, 1H X 0.8 : 1'H₆ 1st isomer)

7.95 (dd, 1H X 0.2 : 1'H₆ 2nd isomer)

20 An aqueous solution at a concentration of 10% of 5 δ -[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin 1_A (product AD), in the form of hydrochloride, is obtained with:

25 product AD 0.1 g
 0.5 N hydrochloric acid 0.38 cc
 distilled water .. q.s. 1 cc

REFERENCE EXAMPLE 20

By using a method similar to that described in Reference Example 16, but starting from 5 δ -methylenepristinamycin I_A (4 g) and 1,3-bisdimethylamino-2-propanethiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 20 to 60 to dryness under reduced pressure (2.7 kPa) at 30°C, 5 δ -[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin I_A (0.59 g) is obtained in the form of a white powder melting at about 170°C.

NMR spectrum:

0.63 (dd, 1H : 5 β ₂)

2.40 (s, 6H : -N(CH₃)₂)

2.50 (m, 10H : $\begin{array}{c} \text{CH}_2\text{N} < \\ | \\ -\text{CH} < \\ | \\ \text{CH}_2\text{N} < \end{array}$ + -N(CH₃)₂)

4.97 (s, 1H : 5 ϵ ₁)

5.30 (m, 2H : 5 α + 4 α)

7.85 (mt, 1H X 0.85 : 1'H₆ 1st isomer)

7.95 (mt, 1H X 0.15 : 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 7.5% of 5 δ -[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin I_A (product AE), in the form of hydrochloride, is

obtained with:

product AE	0.03 g
0.1 N hydrochloric acid	0.3 cc

distilled water .. q.s.0.4 cc

REFERENCE EXAMPLE 21

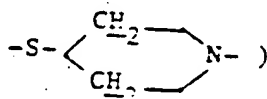
By using a method similar to that described in reference Example 16, but starting from 5 δ -methylenepristinamycin I_A (3 g) and 2-methyl-4-mercaptopiperidine (0.97 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 10 to 16 to dryness under reduced pressure (2.7 kPa) at 30°C, 5 δ -(1-methyl-4-piperidyl)thiomethylpristinamycin I_A (1.1 g) is obtained in the form of a white powder melting at 260°C.

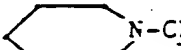
NMR spectrum:

0.6 (dd, 1H : 5 β ₂)

15

2 (m, 4H :

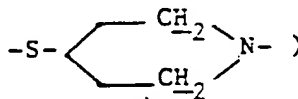


2.20 (s, 3H : -S-N-CH₃)

2.35 (m, 1H : 5 β ₁)

20

2.90 (m, 4H :



5.30 (m, 2H : 5 α + 4 α)

7.85 (dd, 1H : 1'H₆)

An aqueous solution at a concentration of 5% of 5 δ -(1-methyl-4-piperidyl)thiomethylpristinamycin I_A (product AF), in the form of hydrochloride, is obtained with:
product AF 0.03 g

0.1 N hydrochloric acid 0.3 cc
distilled water .. q.s. 0.6 cc

REFERENCE EXAMPLE 22

By repeating Reference Example 16, but starting
5 from 5 δ -methylenepristinamycin I_A (2 g) and 2-diethyl-
aminoethanethiol (0.66 g), after purification by "flash"
chromatography [eluent: chloroform-methanol (95-5 by
volume)], and concentrating fractions 9 to 18 to dryness
under reduced pressure (2.7 kPa) at 30°C, 5 δ -(2-diethyl-
10 aminoethyl)thiomethylpristinamycin I_A (0.8 g) is obtained
in the form of a beige powder melting at 230°C.

NMR spectrum:

0.65 (dd, 1H : 5 β ₂)

2.38 (d, 1H : 5 β ₁)

15

2.3 to 2.8 (m, 8H : -S CH₂CH₂ N $\begin{matrix} \text{CH}_2^- \\ \text{CH}_2^- \end{matrix}$)

3.15 (dd, 1H : -CH₂S-)

3.35 (dd, 1H : -CH₂S-)

5.01 (dd, 1H : 5 ϵ ₁)

7.81 (dd, 1H X 0.9 : 1'H₆ 1st isomer)

7.90 (dd, 1H X 0.1 : 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 5% of

5 δ -(2-diethylaminoethyl)thiomethylpristinamycin I_A

25 (product AF₁) in the form of hydrochloride, is obtained

with:

product AF₁ 30 mg

0.1 N hydrochloric acid 0.29 cc
distilled water .. q.s. 0.6 cc

CLYK
REFERENCE EXAMPLE 23

P 2-Dimethylaminoethylamine (5.3 g) is added drop-
5 wise, so as not to exceed 25°C, to a solution of 5δ-
dimethylaminomethylenepristinamycin I_A (5.5 g) in acetic
acid (60 cc). The solution obtained is stirred at a tem-
perature of about 20°C for 20 hours and is then poured
slowly into a saturated aqueous solution of sodium bicar-
10 bonate; the mixture obtained is extracted twice with methy-
lene chloride (750 cc in total). The organic phases are
combined, dried over magnesium sulphate, filtered, and
concentrated to dryness under reduced pressure (2.7 kPa)
at 30°C. The residue is purified by "flash" chromato-
15 graphy [eluent: chloroform-methanol (90-10 by volume)];
fractions 10 to 12 are concentrated to dryness under
reduced pressure (2.7 kPa) at 30°C. In this manner
5δ-(2-dimethylaminoethyl)aminomethylenepristinamycin I_A
ex (3 g) is obtained in the form of a beige powder melting
20 at about 180°C.

P NMR spectrum:

25 141 at
0.90 (mt, 4H : 2γ + 5β₂)
2.25 (mt, 6H : -N(CH₃)₂)
2.50 (mt, 3H : -CH₂N< + 5β₁)
3.25 (mt, 2H : >N-CH₂-)
3.50 (mt, 2H : 5ε₂ + 3δ₁)
4.90 (mt, 1H : 5ε₁)

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between 7.15 and 7.4 (m, 1H : $\begin{array}{c} \text{NH-} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H} \end{array}$)

9.90 (mt, 1H (exchangeable with D₂O) : -NH-)

5 *GT* 5δ-(2-dimethylaminoethyl)aminomethylenepristinamycin I_A (product AG) is obtained with:

1421 product AG 0.1 g
distilled water .. q.s. 10 cc

REFERENCE EXAMPLE 24

10 *P* By using a method similar to that described in Reference Example 23, but starting from 5δ-dimethylamino-methylenepristinamycin I_A (13.8 g) and 4-amino-2-methyl-piperidine (3.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (92.5-7.5 by volume)], and concentrating fractions 15 to 20 to dryness under reduced pressure (2.7 kPa) at 30°C, 5δ-(1-methyl-4-piperidyl)aminomethylenepristinamycin I_A (4.0 g) is obtained in the form of a yellow powder melting at 208°C.

P NMR spectrum:

20 0.40 (m, 4H : 2γ + 2β₂)

14201 2.0 (m, 4H : $-\begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2 \end{array} \text{N}-$)

2.35 (s, 3H : >N-CH₃)

2.45 (d, 1H : 5β₁)

2.90 ($-\begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2 \end{array} \text{N}-$)

3.20 (under unresolved bands, 1H : $-\text{CH}-\text{N}-$)

3.50 (d, 1H : 5E₂)

4.85 (under unresolved bands, 1H : 5E₁)

6.65 (d, 1H : =CHNH-)

5 9.70 (dd, 1H X 0.15: =CH-NH- 1st isomer)

10.03 (dd, 1H X 0.85 : =CH-NH- 2nd isomer)

An aqueous solution at a concentration of 10% of 56-(1-methyl-4-piperidyl)aminomethylenepristinamycin I_A (product AT), in the form of hydrochloride, is obtained with :

10 *7/14/80*
 product AT 0.03 g
 0.1 N hydrochloric acid 0.3 cc
 distilled water .. q.s. 0.3 cc

8 4-Amino-2-methylpiperidine can be prepared by the method described by E.F. Elslager, L.M. Werbel, A. Curry, 15 N. Headen, J. Johnson, J. Med. Chem. 17, 99 (1974).



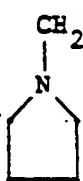

By using the method of Reference Example 23, the following synergistins of general formula (V), which can be combined with the products according to the invention, are prepared.



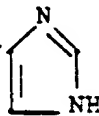
B 20 *8* [The symbols --- , X and Z are defined as at 2b) for the general formula (V) and, unless stated otherwise, Y denotes a dimethylamino radical].

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Reference example	R ₄	1) Melting point 2) Solubility
25	$-\text{NH}-(\text{CH}_2)_2\text{N}(\text{C}_2\text{H}_5)_2$	1) Yellow powder M abt. 150°C 2) 5% aqueous solution as hydrochloride
26	$-\text{NH}(\text{CH}_2)_2\text{NHCH}_3$	1) Yellow powder M = 174°C 2) 1% aqueous solution as hydrochloride
27	$-\text{NH}(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	1) Yellow powder M abt. 155°C 2) 6.6% aqueous solution as hydrochloride
28	$\begin{array}{c} -\text{NH}-\text{CH}-\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array}$	1) Yellow powder M abt. 160°C 2) 1% aqueous solution as hydrochloride
29	$\begin{array}{c} -\text{NHCH}_2\text{CH}-\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array}$	1) Orange powder M abt. 175°C 2) 10% aqueous solution as hydrochloride
30	$\begin{array}{c} -\text{NH}-\text{CH}-(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2 \\ \\ \text{CH}_3 \end{array}$	1) Beige powder M abt. 160°C 2) 1% aqueous solution as hydrochloride
31	$-\text{NH}-(\text{CH}_2)_2-\text{N} \begin{array}{ c } \hline \diagup \quad \diagdown \\ \hline \end{array}$	1) Yellow powder M = 183°C 2) 1% aqueous solution as hydrochloride
32	$-\text{NH}(\text{CH}_2)_3-\text{N} \begin{array}{ c } \hline \diagup \quad \diagdown \\ \hline \end{array}$	1) Yellow powder M = 170°C 2) 1% aqueous solution

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Reference example	R ₄	1) Melting point 2) Solubility
33	$\text{-NH(CH}_2\text{)}_2\text{-N}$ 	1) Yellow powder M = 162°C 2) 1% aqueous solution as hydrochloride
34	$\text{-NH(CH}_2\text{)}_2\text{-N}$ 	1) Beige powder M abt. 172°C 2) 1% aqueous solution as hydrochloride
35	$\text{-NH-CH}_2\text{-}$ 	1) Beige powder M abt. 160°C 2) 1% aqueous solution as hydrochloride
36	-NH- 	1) Beige powder M = 177°C 2) 1% aqueous solution as hydrochloride

Reference example	Y	R ₄	1) Melting point 2) Solubility
37	H	-NH-  -N-CH_3	1) Beige powder M abt. 195°C 2) 5% aqueous solution as hydrochloride
38	$\text{-N(CH}_3\text{)}_2$	$\text{-NH(CH}_2\text{)}_2\text{-N}$  -N-CH_3	1) Yellow powder M = 150°C 2) 10% aqueous solution as hydrochloride
39	$\text{-N(CH}_3\text{)}_2$	$\text{-NH-(CH}_2\text{)}_2\text{-}$ 	1) Yellow powder M = 138°C 2) 10% aqueous solution as hydrochloride

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REFERENCE EXAMPLE 40

CLYK
2-Dimethylaminoethanethiol (2.1 g) is added to a solution of 5 δ -dimethylaminomethylenepristinamycin I_A (1.84 g) in acetic acid (40 cc). The solution obtained is stirred at a temperature of about 20°C for 20 hours and is then poured slowly into a saturated aqueous solution of sodium bicarbonate; the mixture obtained is extracted 3 times with methylene chloride (400 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (96-4 by volume)]; fractions 5 and 6 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. In this manner, 5 δ -(2-dimethylaminoethyl)thio-methylenepristinamycin I_A (0.8 g) is obtained in the form of a yellow powder melting at about 150°C.

NMR spectrum:

0.68 (dd, 1H : 5 β 2)
2.32 (s, 6H X 0.85 : -CH₂N(CH₃)₂ 1st isomer),
2.35 (s, 6H X 0.15 : -CH₂N(CH₃)₂ 2nd isomer),
2.45 (d, 1H : 5 β 1)
2.65 (mt, 2H : -SCH₂-)
3.05 (t, 2H : -CH₂N-)
3.43 (dd, 1H : 5 ϵ 2)
5.15 (in unresolved bands: 5 ϵ 1)
7.60 (broad s, 1H : =CHS-)

UNRES
UNRES
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UNRES
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UNRES

7.83 (mt, 1H : 1'H₆, two isomers)

An aqueous solution at a concentration of 1% of 5δ-(2-dimethylaminoethyl)thiomethylenepristinamycin I_A (product AX), in the form of hydrochloride, is obtained


5 with:

14701
product AX 0.1 g
0.1 N hydrochloric acid 1 cc
distilled water .. q.s. 10 cc

By using the method of reference Example 40, the
10 following synergistins of general formula (V) which can be combined with the products according to the invention, are prepared.

ps 8 [The symbols \ominus , X and Z are defined as in 2b) for the general formula (V), and, unless mentioned otherwise, Y
15 denotes a dimethylamino radical].
9

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Reference example	Y	R ₄	1) Melting point 2) Solubility
41	-N(CH ₃) ₂	-S-(CH ₂) ₂ N(C ₂ H ₅) ₂	1) Beige powder M abt. 192°C 2) 1% aqueous solution as hydrochloride
42	-N(CH ₃) ₂	-S-(CH ₂) ₃ N(CH ₃) ₂	1) Beige powder M abt. 170°C 2) 1% aqueous solution as hydrochloride
43	-H	-S(CH ₂) ₃ N(CH ₃) ₂	1) Beige powder M abt. 140°C 2) 10% aqueous solution as hydrochloride
44	-N(CH ₃) ₂	-S-CH ₂ -CH-CH ₂ N(CH ₃) ₂ CH ₃	1) Beige powder M = 234°C 2) 10% aqueous solution as hydrochloride
45	-N(CH ₃) ₂	-S-CH ₂ -C-N(CH ₃) ₂ CH ₃ CH ₃	1) Beige powder M abt. 200°C 2) 1% aqueous solution as hydrochloride
46	-N(CH ₃) ₂	-S(CH ₂) ₂ -N 	1) Beige powder M abt. 180°C 2) 1% aqueous solution as hydrochloride

148a

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Reference example	R ₄	1) Melting point 2) Solubility
47	$-S-(CH_2)_2-\overset{\overset{CH_3}{ }}{\underset{\text{N}}{\text{C}_4\text{H}_8}}$	1) Beige powder M abt. 215°C 2) 0.6% aqueous solution as hydrochloride
48	$-S-\text{C}_6\text{H}_{10}-N-CH_3$	1) Yellow powder M abt. 170°C 2) 1% aqueous solution as hydrochloride
49	$-S-\text{C}_6\text{H}_{10}-N-CH_2CH_3$	1) Beige powder M abt. 175°C 2) 1% aqueous solution as hydrochloride
50	$-S-(CH_2)_2N-(CH_2)_2N(CH_3)_2$	1) Yellow powder M abt. 160°C 2) 1% aqueous solution
51	$-S-CH[CH_2N(CH_3)_2]_2$	1) Beige powder M abt. 190°C 2) 1% aqueous solution as hydrochloride
52	$-S(CH_2)_2-N\text{C}_6\text{H}_{10}-N-CH_3$	1) Beige powder M abt. 170°C 2) 1% aqueous solution as hydrochloride
53	$-S(CH_2)_3-N\text{C}_6\text{H}_{10}-N-CH_3$	1) Beige powder M abt. 190°C 2) 10% aqueous solution as hydrochloride
54	$-S-CH_2-\underset{\overset{CH_3}{ }}{CH}-CH_2-\overset{\oplus}{N}(CH_3)_3$	1) Ochre powder M abt. 150°C 2) 1% aqueous solution as hydrochloride
55	$-S(CH_2)_2SO_3H$	1) Yellow powder M > 280°C 2) 5% aqueous solution

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REFERENCE EXAMPLE 56

A solution of 5 δ -(4-methylphenyl)sulphonyloxy-
 methylenepristinamycin I_A (5.2 g) in methylene chloride
 (50 cc) is added to a solution of 1-(2-mercaptopropyl)-
 4-methylpiperazine (0.87 g) in ethanol (50 cc), to which
 sodium ethoxide (0.34 g) has been added. The reaction
 mixture is stirred at a temperature of about 20°C for
 16 hours and is then diluted with methylene chloride
 (500 cc) and distilled water (100 cc). After stirring,
 the aqueous phase is extracted twice with methylene
 chloride (50 cc in total). The organic phases are com-
 bined, dried over magnesium sulphate, filtered, and then
 concentrated to dryness under reduced pressure (2.7 kPa)
 at 30°C. The residue is purified by "flash" chromato-
 graphy [eluent: chloroform-methanol (97.5-2.5 by volume)].
 Fractions 33 to 80 are combined and concentrated to dry-
 ness under reduced pressure (2.7 kPa) at 30°C. In this
 manner, 5 δ -[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethy-
 lenepristinamycin I_A (1.25 g) is obtained in the form
 of a beige powder melting at about 195°C.

NMR spectrum:

0.70 (dd, 1H : 5 β 2)

1.25 (d, 3H : -CH-CH₃)

2.30 (s, 3H : >N-CH₃)

2.50 (m, 10H : -CH₂-N(CH₂CH₂)₂-N-CH₃)

25

180 at

1-3

3.40 (dd, 1H : 5E₂)

7.85 (broad dd, 1H : 1'H₆)

An aqueous solution at a concentration of 10% of 5δ-[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethylenepristinamycin I_A (product AAN) in the form of hydrochloride is obtained with:

product AAN 0.03 g

0.1 N hydrochloric acid 0.3 cc

1-(2-Mercaptopropyl)-4-methylpiperazine is prepared by heating a mixture of propylene sulphide (19 cc) and N-methylpiperazine (29 cc) at 100°C for 16 hours. In this manner, a colourless oil (32 g) which distils at 105°C at 1.3 kPa is obtained.


5δ-(4-Methylphenyl)sulphonyloxymethylenepristinamycin I_A can be obtained as follows:

Triethylamine (0.42 cc), and then p-toluenesulphonyl chloride (0.57 g) are added to a solution of 5δ-hydroxymethylenepristinamycin I_A (2.7 g) in methylene chloride (30 cc), at a temperature of about -30°C. The reaction mixture is then stirred at a temperature of about 20°C for 2 hours and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C; the residue obtained is purified by "flash" chromatography [eluent: methylene chloride-methanol (96-4 by volume)]. After concentrating fractions 4 to 6 to dryness under reduced pressure (2.7 kPa) at 30°C, 5δ-(4-methylphenyl)sulphonyloxymethylenepristinamycin I_A (2.2 g) is obtained in the

form of a white powder melting at about 265°C.

NMR spectrum:

0.50 (dd, 1H : 5β₂)

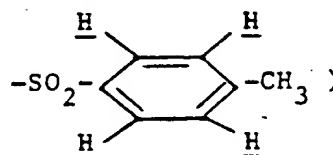
2.35 (s, 3H : -SO₂--CH₃)

3.30 (dd, 1H : 5E₂)

5.25 (d, 1H : 5α)

5.30 (dd, 1H : 5E₁)

7.35 to 7.90 (AB system + m, 8H : 4 δ + 4 ε +



7.85 (dd, 1H : 1'H₆)

5δ-Hydroxymethylenepristinamycin I_A can be prepared as follows:

5δ-Dimethylaminomethylenepristinamycin I_A (10.6 g) is added to a 0.1 N aqueous solution (420 cc) of hydrochloric acid. The solution obtained is then stirred at a temperature of about 20°C for 3 hours. A saturated aqueous solution (30 cc) of sodium bicarbonate is then added dropwise so as to produce a pH of about 4. The product which precipitates is separated off by filtration and is then washed 3 times with distilled water (30 cc in total). After drying under reduced pressure (2.7 kPa) at a temperature of about 20°C, 5δ-hydroxymethylenepristinamycin I_A (9.5 g) is obtained in the form of a beige powder. This product is of adequate quality to be used as such in the subsequent steps. It can, however, be purified as follows:

Crude 5 δ -hydroxymethylenepristinamycin I_A
(9.5 g) is dissolved in ethyl acetate (50 cc); the solu-
tion obtained is poured onto silica gel (100 g) contained
in a column 2.8 cm in diameter. Ethyl acetate (400 cc)
5 is used for the initial elution, and the corresponding
eluate is discarded; elution is then continued with
ethyl acetate (1600 cc), and the corresponding eluate is
concentrated to dryness under reduced pressure (2.7 kPa)
at 30°C. In this manner 5 δ -hydroxymethylenepristina-
10 mycin I_A (6.3 g) is obtained in the form of white crys-
tals melting at 220°C.

NMR spectrum:

0.69 (dd, 1H : 5 β 2)
2.43 (d, 1H : 5 β 1)
3.40 (d, 1H : 5E2)
4.0 to 4.2 (m, 3H : 4X + 5E1 + 5D)
8.15 (s, 1H : =CH-OH)
11.63 (broad s, 1H : =CH-OH)

REFERENCE EXAMPLE 57

By using a method similar to that described in
Reference Example 56, 5 δ -(3-dimethylamino-2-propyl)thio-
methylenepristinamycin I_A (1 g) is obtained in the form
of a yellow powder melting at 172°C.

An aqueous solution at a concentration of 5% of
5 δ -(3-dimethylamino-2-propyl)thiomethylenepristinamycin
I_A, in the form of hydrochloride, is obtained.

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clerk
REFERENCE EXAMPLE 58

P By using a method similar to that described in Reference Example 56, ^{6x}5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin I_A (1.32 g) is obtained in the form of a beige powder melting at about 185°C.

An aqueous solution at a concentration of 10% of ^{6x}5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin I_A in the form of hydrochloride, is obtained.

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REFERENCE EXAMPLE 59

P A solution of 5δ-[(4-methylphenyl)sulphonyloxy-methylene]pristinamycin I_A (7.6 g) in tetrahydrofuran (60 cc) is cooled to a temperature of about -10°C. While maintaining this temperature, a solution is added to it, consisting of 2-dimethylaminoethanol (0.65 g) in tetrahydrofuran (60 cc), to which a 50% strength dispersion (0.35 g) of sodium hydride in mineral oil has been added. When the addition is complete, the temperature is allowed to rise slowly to about 20°C. The reaction mixture is stirred at this temperature for 24 hours and is then diluted with methylene chloride (500 cc) and washed with a saturated solution of ammonium chloride (2 x 50 cc). The organic phase is dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)]. Fractions 12 to 17 are combined and concentrated to dryness under reduced pressure

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(2.7 kPa) at 25°C. In this manner, 5~~8~~-(2-dimethylaminoethoxymethylene)pristinamycin I_A (1.5 g) is obtained in the form of a beige powder melting at about 160°C.

NMR spectrum:

0.65 (dd, 1H : 5~~8~~2),
2.3 (s, 6H : -N(CH₃)₂),
2.65 (m, 2H : -CH₂N<),
3.42 (dd, 1H : 5~~8~~2),
4.15 (t, 2H : -OCH₂-),
5.15 (d, 1H : 5~~8~~1),
7.45 (under the aromatics, 1H : >C=CH-O-),
7.80 (dd, 1H : 1'H₆)

An aqueous solution at a concentration of 1% of 5~~8~~-(2-dimethylaminoethoxymethylene)pristinamycin I_A (product AAQ), in the form of hydrochloride, is obtained with:

product AAQ 0.03 g
0.1 N hydrochloric acid 0.3 cc
distilled water .. q.s. 3 cc

The present invention also relates to the medications consisting of a product of general formula (I) in free form or preferably in the form of a salt of addition with a pharmaceutically acceptable acid in the form of a combination with known synergists or preferably with synergists of general formula (V), the combination being moreover capable of containing any other pharmaceutically compatible, inert or physiologically active, product.

The medications according to the invention can be

administered by parenteral, oral, rectal or topical route.

Sterile compositions for parenteral administration can be, preferably, aqueous or nonaqueous solutions, suspensions or emulsions. Water, propylene glycol, a poly-
5 (ethylene glycol), vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents, can be used as a solvent or vehicle. These compositions can also contain adjuvants, especially wetting agents, isotonizing agents,
10 emulsifiers, dispersants and stabilizers. Sterilization can be carried out in various ways, for example by an asepticizing filtration, by adding sterilizing agents to the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions
15 which can be dissolved in an injectable sterile medium at the time of use.

Tablets, pills, powders or granules can be employed as solid compositions for oral administration. In these compositions, the active product according to the invention
20 (optionally combined with another pharmaceutically compatible product) is mixed with one or more inert diluents or adjuvants such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, for example a lubricant such as magnesium stearate.

25 Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents such as water or paraffin oil can be used as liquid

compositions for oral administration. These compositions can also comprise substances other than the diluents, for example wetting agents, sweeteners or flavourings.

5 Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active substance, excipients such as cocoa butter, semi-synthetic glycerides or poly(ethylene glycols).

10 Compositions for topical administration can be, for example, creams, salves, lotions, eye lotions, mouth washes, nasal drops or aerosols.

15 In human therapy, the products according to the invention, which are combined with known synergists or preferably with synergists of general formula (V), are especially useful in the treatment of infections of a microbial origin. The dosages depend on the required effect and on the duration of treatment; for an adult, they are generally between 500 and 2000 mg per day by parenteral route, especially by an intravenous route such as a slow perfusion, the dosage of synergist of general formula
20 (V) itself being between 500 and 2000 mg per day.

 As a general rule, the practitioner will determine the dosage which he or she considers the most suitable, depending on the age, weight and all the other individual characteristics of the subject to be treated.

25 The following example, given without implying any limitation, illustrates the compositions according to the invention.

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EXAMPLE

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

- 5 - 26-(2-diethylaminoethyl)sulphinyl-
pristinamycin II_B 0.6 g
- 5 δ -[2-(4-methyl-1-piperazinyl)ethyl]-
thiomethylpristinamycin I_A 0.4 g
- 0.1 N aqueous solution of hydrochloric acid .. 12.7 cc
10 - distilled water .. q.s. 1000 cc
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